

A stylized white line art illustration of a woman's profile, facing right. The illustration is set against a solid salmon-colored background. The woman's hair is styled in an updo, adorned with various floral and leaf motifs. A large, stylized leaf or petal shape frames the left side of her face. The overall aesthetic is clean and modern.

DIAGNOSTIC DELAY OF ENDOMETRIOSIS

Moniek van der Zanden

Diagnostic delay of endometriosis

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The research presented in this thesis was conducted at the department of obstetrics and gynaecology of the Radboud university medical center, Nijmegen, the Netherlands, within the Radboud Institute for Health Sciences.

For reasons of consistency within this thesis, some terms have been standardised throughout the text. As a consequence the text may differ from the articles that have been published.

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Diagnostic delay of endometriosis

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Endometriosis is defined as the presence of endometrial-like tissue (glands and stroma) outside the uterus, which induces a chronic inflammatory reaction.¹ The condition is estrogen-dependent and predominantly found in women in their reproductive life span. It is one of the most common benign gynaecologic conditions. The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% within the general female population up to 50% in women presenting with subfertility or chronic pelvic pain.²⁻⁵ The clinical presentation can be highly variable. Endometriosis may be suspected based on a woman's history, symptoms and signs; the diagnosis is affirmed by findings in physical examination and imaging techniques, and finally proven by histology of either a biopsy from a directly visible lesion or tissue collected during laparoscopy.⁴ The disease negatively affects several aspects of women's lives, including their physical and emotional wellbeing, social roles and ability to work.⁶⁻⁸ Besides the impact on individual quality of life, the cost of endometriosis is a burden to society due to medical costs of treatment and economic costs because of the inability to work, which is comparable to other chronic conditions like diabetes mellitus.⁸

Etiology

Although endometriosis is one of the most commonly encountered problems in gynaecology, its pathogenesis is still poorly understood and remains controversial. The discovery of the condition is a topic of debate as well.⁹⁻¹¹ Microscopic findings in line with the present understanding of endometriosis were first described by the Czech pathologist Karl von Rokitansky in 1860, reporting about endometrial glands and stroma present in ovarian and uterine neoplasias.¹² The full morphological and clinical picture of endometriosis (and adenomyosis) was first described by the surgeon Thomas Cullen in 1908.¹³ However, it was John Sampson who created the name "endometriosis". His original observation came when he operated women at the time they were menstruating, and observed that the peritoneal lesions were bleeding.¹⁴ In 1927, Sampson postulated that the presence of endometrial cells outside the uterus was due to tubal dissemination of menstrual shedding.¹⁴

There are three main concepts with regard to the pathogenesis of endometriosis: 1) the in situ development theory, the concept that endometriosis develops from local tissues, such as the germinal epithelium of the ovary, remnants of the Wolffian or Müllerian ducts or from metaplasia of mesothelial cells lining the pelvic peritoneum, 2) the induction theory, the

concept that endogenous substances released from degenerating menstrual endometrium induce a metaplastic process in coelomic epithelium covering the ovary and the serosa of the peritoneum to develop into endometrial tissue and 3) Sampson's retrograde menstruation theory, which is currently considered the most widely accepted theory regarding the pathogenesis of endometriosis. According to this theory, reflux of viable endometrial cells through the fallopian tubes occurs during menstruation. Once these cells reach the peritoneal cavity, they can implant, grow and invade into pelvic structures. However, menstrual reflux through the fallopian tubes into the peritoneal cavity is a common physiologic event in all menstruating women with patent tubes, and subtle lesions occur frequently in asymptomatic women.¹⁵⁻¹⁷ This has led to the hypothesis that mild peritoneal endometriosis may be considered a temporarily physiologic phenomenon rather than a disease.¹⁷ In women with an incapacity to clear the peritoneal cavity, the endometrial cells and lesions may have the opportunity to adhere, vascularize, grow and invade surrounding structures and organs. Why these endometrial cells and implants are resolved by the immune system in some women, whilst other women appear incapable of clearing the peritoneal cavity remains unclear.¹⁸ It is suggested that several epidemiological and biological factors affect this process. One of these factors is the reproductive and menstrual pattern of women, which has changed over the last decades, at least in Western nations, due to the decrease in number of pregnancies and duration of breastfeeding, and increased life expectancy. This has led to an increased number of ovulations and menstrual flows, which have been linked to a higher risk of developing endometriosis.^{19, 20} Other determinants, including (epi)genetic factors and biological factors related to molecular and cellular alterations that favour the progression of cell implantation and growth at ectopic locations may be involved in the development of endometriosis as well.¹⁸ Finally, there is accumulating evidence that adult stem cells are involved in the pathogenesis of endometriosis. These cells can either originate from the endometrium or directly from the bone marrow entering the peritoneal cavity by hematogenous or lymphatic dissemination.²¹ A stem cell origin of endometriosis may be the missing link between some of the previously postulated theories on pathogenesis, since endometriosis could arise from the retrograde menstruation of endometrial stem cells, the dissemination of stem cells derived from bone marrow or endometrium and/or stem cells in persistent Müllerian remnants. Efforts are still being made to further elucidate the exact pathogenesis of endometriosis. This is of major importance, since it may reveal new targets for the development of treatment regimens.

Epidemiology

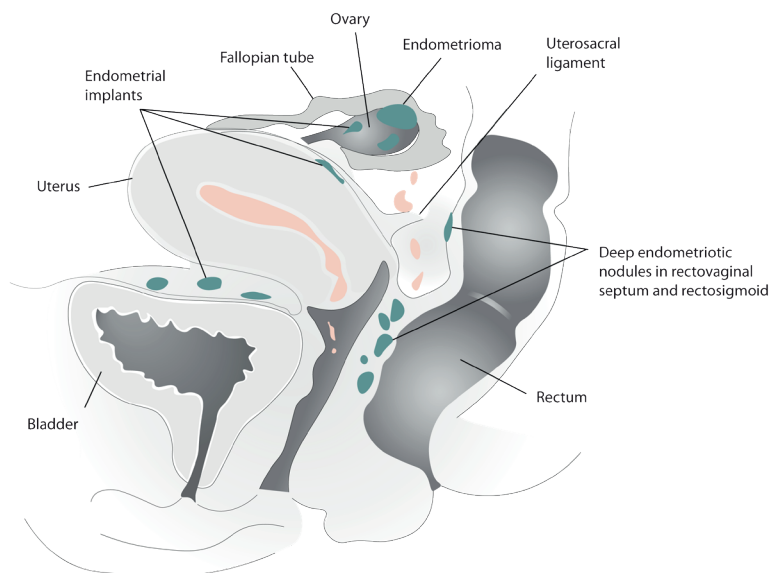
As stated before, the estimated prevalence rate of endometriosis is 10% in the general female population. A wide variety in prevalence is seen in different studies, which may be influenced by the type of study population or the diagnostic criteria applied.^{2, 3, 20, 22-24} The high estimates are derived from a selection of women undergoing laparoscopic tubal ligation, and include women with asymptomatic endometriotic lesions that did not require treatment.⁵ On the other hand, literature from the general population reported relatively low prevalence rates.^{22, 25} These studies rely on completeness of coding in medical records or databases, and potentially exclude asymptomatic women or those with only mild to moderate symptoms who did not receive full diagnostic tests or treatment, as well as women with limited access to healthcare, for instance because of low socio-economic status and lack of insurance. Moreover, many women with symptoms suggestive of endometriosis either receive a false diagnosis, for instance irritable bowel disease, or respond well to pragmatic medical treatment and may not proceed towards diagnostic or therapeutic laparoscopy, and therefore do not have a confirmed diagnosis which hampers the accuracy of administrative studies.

Endometriosis is seen predominantly in women of reproductive age. There appears to be a peak in diagnosis between age 25 and 35 years old.^{22, 24, 26} Risk factors are prolonged or extensive exposure to menstrual flow, the presence of Müllerian duct anomalies and cervical or vaginal obstruction, and a positive family history.^{18, 20, 27} There is no convincing evidence that prevalence rates vary with race or ethnicity. Early studies suggested that endometriosis is infrequent in Black women as well as those of low socio-economic status, but they are likely to be influenced by methodological and social bias, and may reflect a limited ability to access healthcare, in particular advanced and expensive diagnostic or therapeutic regimens.²⁸

Types of endometriosis

Three distinct clinical forms of pelvic endometriosis can be distinguished: peritoneal, ovarian and deep endometriosis (figure). Peritoneal endometriosis is defined as the presence of characteristic superficial implants on the pelvic peritoneum. The peritoneal lesions can only be visualized at laparoscopy and may have many variable appearances. They can provoke an inflammatory response and cause adhesions in the abdominal cavity. Ovarian endometriosis

is characterized by the presence of ovarian cysts also referred to as endometrioma. Deep endometriosis is defined as endometriosis deeper than 5 mm under the peritoneal surface. It includes nodules and plaques which can involve and infiltrate several organs and structures, including (but not limited to) the parametria, uterosacral ligaments, pouch of Douglas, the rectovaginal septum, bladder, ureters and rectosigmoid. Endometriotic lesions can be observed at locations outside the pelvis as well, such as the liver, diaphragm, pleura, lung and umbilicus, although these structures are less frequently involved as compared to pelvic structures. Depending on the size, location and depth of infiltration, the lesions can cause severe pain and impairment in function of affected organs.



Clinical presentation and diagnosis

Signs and symptoms

Dysmenorrhea, dyspareunia, chronic pelvic pain and subfertility are considered characteristic symptoms of endometriosis. Women with endometriosis may present with one or more of these complaints, while others are completely asymptomatic. However, a wide variety of symptoms may be presented, with many of them rather prevalent in young women, non-specific or overlapping

with other conditions. These include cyclical urinary or intestinal complaints (dysuria, dyschezia, periodic bloating, diarrhea or constipation), excessive or irregular menstrual bleeding, fatigue, referred pain in the back or legs and many more.^{4, 24, 29, 30} Dysmenorrhea appears to be the leading presenting complaint, present in up to 62% of women with endometriosis, followed by chronic pelvic pain (57%), deep dyspareunia (55%), cyclical intestinal complaints (48%), subfertility (40%) and cyclical urinary complaints (12%).³¹ However, these numbers vary between different studies, and the predictive value of any symptom or combination of symptoms remains uncertain as they can have other causes, and a significant proportion of affected women is asymptomatic.^{24, 32, 33} Nevertheless, performing a detailed history in women with abdominal symptoms will help in identifying those with an increased risk of endometriosis in a timely matter.

Physical examination

Clinical examination is aimed at facilitating timely diagnosis and treatment of endometriosis. It includes inspection and palpation of the abdomen and a pelvic examination including visualization of the cervix, posterior fornix and vaginal wall using a speculum, and bimanual palpation of the internal genital organs and rectovaginal septum. A well-performed clinical examination can attribute to the suspicion of deep endometriosis or adnexal mass and direct further diagnostic strategy, but it does not rule out the presence of endometriosis if no abnormalities are found. The positive and negative predictive values of clinical examination for identifying various types of deep endometriosis in experienced hands are 43-100% and 84-98% respectively.³⁴ Clinical examination has the benefits of being easily available at low cost but has some disadvantages as well. There are occasions that vaginal examination is considered inappropriate, for instance in adolescent girls and women with a history of sexual abuse or certain religious beliefs. Furthermore, the pelvic examination can be very painful for some women and should always be performed with caution.

Imaging techniques and biomarkers

In addition to the clinical examination, imaging techniques can be applied to explain underlying symptoms and assess the size and location of specific lesions. Transvaginal ultrasound (with or without bowel preparation) is used as a first line imaging tool for mapping of disease localizations in different compartments of the pelvis, preferably using a systematic approach.³⁵ Diagnostic accuracy of transvaginal ultrasound with regard to the detection

of endometriosis has been found to be superior to clinical examination, especially for ovarian and rectosigmoid involvement. Positive and negative predictive value for detecting deep endometriosis has been estimated at 87-100% and 90-98% respectively, again if performed by experienced operators.³⁴ When deep endometriosis is suspected, magnetic resonance imaging may be helpful to map the extent of the disease prior to surgery, in order to gain information on multifocality of the lesions and infiltration depth of for example the bowel wall.³⁶ Although these imaging techniques have been proven to be useful in the detection of endometriosis, they lack the possibility to identify superficial peritoneal lesions and to collect tissue for histological evaluation, and are therefore not capable of establishing a definite diagnosis. An expanding number of biomarkers retrieved from endometrial tissue, menstrual fluid, serum, plasma or urine have been studied for their use as a non-invasive diagnostic test for endometriosis. Unfortunately, none of them has been clearly proven to be of clinical use.³⁷⁻⁴¹

Laparoscopy

In women with symptoms and signs suggestive of endometriosis it should be considered to start empirical first line medical treatment, such as analgesics and basic hormonal treatment (continuous combined oral contraceptives or progestagens) before resorting to an invasive procedure like laparoscopy to obtain histological proof of the disease.^{4, 42} Arguments to perform a laparoscopy include the woman's wish to have a definitive diagnosis, subfertility, symptoms and signs indicating advanced disease (ovarian endometrioma and deep infiltrating lesions) and/or unresponsiveness to prior medical treatment. Although laparoscopy allows the clinician to confirm or rule out the presence of endometriosis with a high level of accuracy, a clinical diagnosis based on patient history, pelvic examination and imaging techniques is increasingly advocated due to the safety profile and increasing accuracy.⁴² A thorough preoperative work-up can allow for a limited number of laparoscopies, shifting from a merely diagnostic to a comprehensive "see-and-treat" strategy.

Diagnostic delay

Due to the wide variety in symptomatology and the lack of an accurate non-invasive diagnostic test, it has been proven difficult for many clinicians to establish a timely diagnosis of endometriosis. Diagnostic delay in endometriosis is defined as the interval between first onset of symptoms and

eventual diagnosis. Delay in the diagnosis of endometriosis is a significant barrier in the management of this condition, leading to years of suboptimal treatment and possible disease progression.^{43, 44} This is an unfavourable situation, given the impact on physical, emotional and social wellbeing for individual women and the economic burden to society.

Studies addressing the length of the diagnostic delay of endometriosis have reported delays up to eleven years.^{7, 26, 44-48} The first scientific study directed at the diagnostic delay was presented by Hadfield and co-workers in 1996.⁴⁶ They confirmed prior non-published observations from endometriosis self-help groups in a population of patients from the USA and UK, and identified a diagnostic delay of 11.73 and 7.96 years respectively. Nnoaham and co-workers performed a study in 16 hospitals in ten countries throughout the world and found an average diagnostic delay of 6.7 years (range 3.3-10.7 years). The delay was longer in centres with predominantly state-funded health care compared with self- or insurance funded health care. They stated that the delay was mainly due to late referral from primary care physician to gynaecologist. Affected women reported on average seven primary care consultations before specialist referral was effectuated.⁷ A study by Arruda and co-workers identified a young age at onset of symptoms and pelvic pain as presenting symptoms as compared with infertility as relevant factors negatively affecting diagnostic delay.²⁶ This association was seen in other studies as well.^{44, 49} In addition, Hudelist and co-workers found that 74% of patients received at least one false diagnosis prior to surgical confirmation of endometriosis. In this study, misdiagnosis, mothers considering menstruation as a negative event and normalization of dysmenorrhea by patients significantly prolonged the diagnostic delay.⁴⁸ Ballard and co-workers performed a qualitative study in women with endometriosis and identified factors contributing to the diagnostic delay of endometriosis on both the individual patient and medical level.⁴⁵ Potential causes of delay at women's personal level included difficulties in distinguishing between "normal" and "abnormal" menstrual experiences and delayed disclosure of symptoms to family and friends because of embarrassment. Three key factors contributing to the delay at the medical level were identified: normalization of pain by family doctors, intermittent use of contraceptives causing hormonal suppression of symptoms and the use of non-discriminatory investigations. Furthermore, the importance of receiving a diagnosis as explanation for their often disabling symptoms was stressed by the participating women, since this provided them with a language in which to discuss their condition, offered possibilities for

management to control symptoms, and facilitated support in the social and employment context.

Qualitative research

To obtain a comprehensive view on the diagnostic delay of endometriosis, studies focusing on quantitative measures such as the extent of the delay and distribution of certain characteristics, although obviously of great importance, do not suffice. There is a need for research that goes beyond numerical matters, directed at the understanding of underlying reasons for this issue. Therefore, the use of qualitative research methods is of great value for studies regarding the diagnostic delay of endometriosis. Qualitative research is defined as the systematic collection, organization, and interpretation of textual material derived from talk or observation.⁵⁰ It can help bridge the gaps between theory and practice in medicine, and supplement the more traditional quantitative studies.⁵¹ This type of research answers why and how a certain phenomenon may occur rather than how often or how long. Qualitative data are obtained from observation, interviews, focus groups, interactions and many other sources. Interpretive techniques are used to analyze the data according to existing frameworks, or to induce new concepts and theories. The importance of findings derived from qualitative research has been increasingly appreciated.⁵¹

Outline of the thesis

Despite the many studies that have been conducted in the recent decades, the diagnostic delay of endometriosis remains an issue of great concern. The general aim of this thesis is to obtain insight in the factors contributing to the diagnostic delay of endometriosis, and to identify possible interventions to reduce this delay.

The first part of the thesis focuses on the duration of the diagnostic delay of endometriosis in The Netherlands and determinants contributing to the delay from the patients' perspective. **Chapter two** reports on the interval between onset of symptoms and diagnosis of endometriosis in women treated in a hospital with expertise in endometriosis, and on the factors related to this delay. In **chapter three**, the results of a qualitative study are presented, in which patients' experiences regarding the diagnostic process were discussed in focus group interviews.

The second part of the thesis is directed at the general practitioners' perspective. **Chapter four** describes knowledge and clinical strategies with regard to endometriosis in general practitioners. In **chapter five**, barriers and facilitators to the timely diagnosis of endometriosis in primary care are presented, which have been obtained from focus group interviews with general practitioners.

In the third part, gynaecologists' view on diagnostic delay is discussed. **Chapter six** presents the results of a questionnaire study directed at gynaecologist to evaluate their diagnostic and therapeutic strategies, as well as their opinion on factors contributing to the diagnostic delay of endometriosis.

The final part of the thesis is directed at possible interventions to reduce diagnostic delay. **Chapter seven** describes the results of a Delphi study, in which an expert panel comprised of patients and professionals critically assess and prioritize a selection of possible interventions to reduce the interval between onset of symptoms and diagnosis. This study combines the information yielded in the studies presented in the first six chapters, and forges the views of a wide variety of stakeholders into a set of preferred interventions to reduce diagnostic delay. The preceding chapters are discussed in **chapter eight**, in which future perspectives on reducing the delay are debated from a multidimensional point of view.

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Abstract

Background

Endometriosis has a long diagnostic delay that is influenced by varying socio-economic and healthcare factors. In the Dutch situation, these factors are not yet identified. The aim of this study is to determine the length of the diagnostic delay of endometriosis in the Netherlands and to identify which variables affect this delay.

Methods

A retrospective study among 139 patients diagnosed with endometriosis in a secondary care hospital with a specialized multidisciplinary endometriosis team. The diagnostic process was evaluated using a questionnaire-guided telephonic interview.

Results

The median time interval from the onset of symptoms to diagnosis was 89 months or 7.4 years, divided in 7 months patient delay, 35 months general practitioner (GP) delay and 5 months gynaecologist delay. Determinants for a longer diagnostic delay were young age at onset of symptoms, use of oral contraceptives or analgesics prescribed by GP, alternative diagnoses considered by the GP, and cyclic symptoms. Subfertility as presenting symptom resulted in faster diagnosis.

Conclusion

This study shows that the time interval to the diagnosis of endometriosis is long and mainly consists of the period of time the woman consults her first line medical professional.

Introduction

Endometriosis is defined as the presence of functioning endometrial-like glands and stroma outside the uterine cavity, inducing a chronic inflammatory reaction.¹ The estrogen-dependent lesions may be present intraperitoneally, in the ovaries or deep invasively, and are associated with pelvic pain and subfertility. The exact pathogenesis and pathophysiology are largely unknown.^{2,3} Several groups report on the prevalence of endometriosis, with numbers ranging from 1.9 to 20.7% until up to 50% in subfertile women.⁴⁻⁸ Due to the wide variety in presentation and severity of symptoms, clinicians frequently experience difficulties in diagnosing endometriosis. This results in delayed or suboptimal care for many women with endometriosis.¹ The classical symptoms of endometriosis are dysmenorrhea, cyclic pelvic pain and dyspareunia. However, numerous other often aspecific symptoms have been reported.⁹ The disease has a large impact on the quality of life and is associated with extensive physical and psychological morbidity.¹⁰⁻¹⁴ Moreover, the cost of endometriosis is a burden to society due to medical costs of treatment and economic costs because of the inability to work.^{11,15} Diagnostic delay is unwanted, as in a part of the women with endometriosis, both symptoms and disease may progress without treatment, although evidence is contradictory.¹⁶⁻¹⁸ Various studies show a median diagnostic delay ranging from 2 years to 10.7 years.^{11,15,19-21} A number of causes for the variation in time to diagnosis have been identified. When women present with subfertility, time to diagnosis is relatively short, whereas in women presenting with pain as leading symptom, the time to diagnosis is longer.^{11,22} Moreover, both cultural and healthcare system-related factors are responsible for the difference in time to diagnosis between countries. The attitude towards menstruation and whether pain during menstruation is acceptable are factors that play a role in the time to diagnosis of endometriosis.^{11,19} Nnoaham et al. showed a difference between public- and private-funded healthcare centers.¹⁵ It is unknown how these factors may play a role in the time to diagnosis of endometriosis in the Netherlands.

The general practitioner (GP) fulfils a gatekeeper role in the Netherlands. Self-referral to a specialist is not reimbursed by the healthcare insurance. Therefore, in case of a health problem, people go to see their GP first. The main approach of the GP is to diagnose and treat the disease. Only when a diagnosis cannot be made or treatment has insufficient effect, the GP decides that a patient should consult a second-line medical specialist.

Women presenting with subfertility will be referred to a gynaecologist. Women presenting with abdominal pain may also be referred to other specialists like a surgeon or urologist. In this study, we investigated the time taken to make a diagnosis of endometriosis in a Dutch population of women treated in a secondary care centre. Second, we identified factors contributing to diagnostic delay. Eventually, we aimed at improving the care for women with endometriosis by minimizing the time to diagnosis.

Materials and Methods

Data Collection

In this retrospective study, all patients who were diagnosed with endometriosis by surgery or MRI in Rijnstate hospital Arnhem between March 2012 and April 2014 were selected ($n = 139$). Rijnstate is a secondary referral centre, specialized in multidisciplinary treatment of endometriosis. It is recommended by the Dutch endometriosis society, the endometriosis patient interest group. In our study, age younger than 18 or insufficient understanding of the Dutch language was the exclusion criterion. Patients were informed by mail and, after consent, administered a telephonic questionnaire in May or June 2014. A 15-item questionnaire, developed by XS and AN, incorporated questions about the time of onset of symptoms, time to consultation of their GP, time to referral to a second-line medical specialist, and time to diagnosis. Data were completed with documentation from the patient record. Other questions regarded symptoms, treatment received from the GP, other diagnoses that were considered, and indication for referral. Type of endometriosis was determined by review of the operation reports or the MRI report.

Analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM Corp, Armonk, N.Y., USA). Mann–Whitney U test, Pearson's correlation and Fisher's exact test were used to analyze the data. A p value <0.05 was considered statistically significant. Patients were subdivided in separate groups based on the duration of diagnostic delay by GP and by the gynaecologist. For these analyses, patient groups were split in a short and long diagnostic delay group, which was defined as ≤ 1 or >1 year.

Ethical Approval

Study design was approved by the local ethics committee. An information letter about the study was sent to the participants at least 1 week before

telephonic contact. Consent was obtained from all women included in the analysis.

Results

Ninety three patients of the 139 that were selected completed the full questionnaire. One patient was excluded because of a language barrier. Five women did not give consent to participate in the study. Of these, 2 women preferred not to participate because of the emotional stress associated, 2 women did not give permission to review their record, and 1 woman refrained because she was discontented with the working of the hospital. Forty women were not reached by phone after at least 4 attempts.

The median age at onset of symptoms was 20 (range 14–29) and median age at diagnosis was 31 (range 28–34). Women consulted their GP because of various complaints. The most frequent complaint was dysmenorrhea ($n = 51$). Besides dysmenorrhea, continuous abdominal pain ($n = 9$), subfertility ($n = 6$), dyspareunia ($n = 1$), atypical gynaecologic complaints like menorrhagia ($n = 10$) and atypical non-gynaecologic complaints like dysuria and syncope ($n = 16$) were mentioned.

The median total diagnostic delay was 89 months (interquartile range 25–169), that is, 7.4 years. The median patient delay was 7 months, GP delay was 35 months and gynaecologist delay was 5 months. Diagnostic delay was shorter for patients who consulted their GP because of subfertility as compared to patients with pain-related reasons for seeking medical help (median delay of 21 vs. 100 months, $p = 0.024$).

An extended period of time from first GP visit to referral to a gynaecologist was significantly associated with young age at developing symptoms ($p < 0.001$). Considering one or more other diagnoses before endometriosis, cyclic symptoms, use of oral contraceptives because of dysmenorrhea, and use of analgesics were significantly correlated with extended time from GP presentation to referral to a gynaecologist. This sub-analysis additionally shows an extended time from GP to referral when symptoms were considered common menstrual pains ($p < 0.001$) or were falsely attributed to irritable bowel syndrome ($p = 0.014$) or somatisation ($p = 0.021$). A longer patient delay was associated with a longer GP delay (4 vs. 12 months, $p = 0.028$). Type of endometriosis did not relate to the time from first GP contact until

referral ($p = 0.571$). Time from referral to a gynaecologist to diagnosis was not influenced by presenting symptoms, previous treatment, or by other diagnoses that were considered first.

Discussion

This study shows a median diagnostic delay of 89 months or 7.4 years from first presentation of symptoms to the diagnosis of endometriosis. Previous studies in different European countries show a comparable diagnostic delay. This delay is a combination of patient's and doctor's delay. The patient's delay, with a median length of 7 months, is comparable with previous studies. The most striking result in this study is the long delay caused at the doctor's end. The median GP interval in this study was found to be 35 months, which is by far the largest part of the total delay in diagnosis. Compared to previous reports, we show a relatively long GP interval and a relatively short gynaecologist interval.^{15,19,20,23} We hypothesize that this finding can be explained by the position of the GP in the Dutch healthcare system. Women who are referred to a gynaecologist have a relatively high probability of suffering from a disease. In a healthcare system in which the role of the GP is absent or less prominent, the gynaecologist is consulted by an unselected patient population. In such a healthcare system, the same difficulties may be encountered in distinguishing between healthy and ill individuals as in the GP-centred situation in the Netherlands.

Diagnostic delay is shown as the median, because the length of the diagnostic delay is not distributed normally. By using this method, the influence of outliers is decreased. This also explains why the intervals do not add up to the total diagnostic delay.

In this study, selection bias may be present because women, responding well to oral contraceptives or analgesics prescribed by their GP may not have been diagnosed with endometriosis, have not been referred to a gynaecologist, and therefore, are not included in this study. Besides that, patients with symptoms that have not been recognized by the GP or by the gynaecologist will not have been diagnosed and have not been included in the study either. Prescription of oral contraceptives or pain relief by the GP is associated with a significantly longer time interval from first GP visit to referral to a second-line medical specialist, resulting in an extended overall diagnostic delay. This finding may be a consequence of the alleviation of symptoms by these drugs,

making referral not indicated. The diagnosis endometriosis will therefore not be made immediately in these patients. This is not, by definition, a negative factor. Only when the effect of medication is insufficient, a proper diagnosis and more adequate treatment should be aimed at.

A long patient's delay is associated with a long doctor's delay, as is the case in the presence of relatively mild initial symptoms, a younger age at onset of symptoms, and presentation with cyclic symptoms only. Both patients and doctors may be willing to accept these symptoms for a period of time, explaining them as common menstrual pains.

The consideration of alternative diagnoses, including IBS and somatisation, is related to a long diagnostic delay. The fact that women with endometriosis often present with symptoms including abdominal pain, dyspareunia, dyschezia or dysuria may be responsible for the consideration of other diagnoses first. This study shows that when the first-line medical professional recognizes endometriosis-associated symptoms, referral to a gynaecologist and subsequent additional diagnostic testing are implemented quickly and the diagnosis is made within 5 months. Recognition of endometriosis-associated symptoms by the first-line medical professional is thus crucial for early diagnosis. It is important to understand why certain factors lead to the failure of recognition of endometriosis associated symptoms.

After finishing the interview, a majority of patients spontaneously pointed out that the fact that a study had been undertaken concerning the diagnostic delay of endometriosis made them feel understood better and taken more seriously. Moreover, they felt that participating in the study helped them to emotionally deal with the disease. This, and the finding that some patients refused to take part in the study because they found it too hard to talk about their disease, illustrates that the long time until recognition of their symptoms as a disease may be a traumatizing experience and that attention is found helpful by patients.

In conclusion, this study shows that the time interval to the diagnosis of endometriosis is long and consists of a patient's delay of 7 months, a first-line medical professional's delay of 35 months and a second-line medical professional's delay of 5 months. The presence of aspecific symptoms may cause the first-line medical professional to be more susceptible to biases in the diagnostic process leading to diagnostic delay in endometriosis. More

research is necessary in order to identify flaws in the diagnostic process in endometriosis. Identification of these flaws should lead to improvement of education concerning symptomatology of endometriosis as well as awareness of the diagnostic process itself. Currently, we are carrying out investigations among Dutch GPs about their knowledge on endometriosis and their diagnostic strategies in women with endometriosis.

Funding or Conflict of Interest

None to declare

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Abstract

Objective

To identify strengths and weaknesses in the current diagnostic process of endometriosis from the patients' experience

Design

Qualitative study

Setting

Group interviews throughout the country

Population: Women between 18 and 45 years old who had been diagnosed with endometriosis in the past five years.

Methods

Semi-structured focus group discussions, audio recorded and fully transcribed. Grounded theory methodology was applied for data analysis.

Main outcome measures

Factors related to the diagnostic delay of endometriose and possible interventions to reduce the delay

Results

23 women participated in six focus groups. Mean time from start of symptoms to diagnosis was 101.7 months. Dominant themes were knowledge about normal menstruation and endometriosis in both the general population, being believed and acknowledged by medical staff, and collaboration between health care providers including fast referral to a gynaecologist. Barriers to a timely referral and diagnosis were young age, normalisation of symptoms and a lack of awareness in general practitioners. Facilitating factors were adequate knowledge and skills of the general practitioner, a desire for pregnancy and persisting in a request for specialist consultation by the patient.

Conclusions

The diagnostic process in endometriosis is hampered by late presentation of symptoms to a medical professional, inadequate appraisal of symptoms and the interaction between patients and medical professionals. Efforts should be made to increase awareness in the general population, and to provide

medical staff with sufficient knowledge and skills to adequately acknowledge presented symptoms or clinical findings and initiate appropriate actions.

Introduction

Endometriosis is one of the most prevalent gynaecologic conditions in women of reproductive age, and the most common cause of chronic pelvic pain.¹⁻³ Symptoms related to endometriosis commonly include dysmenorrhoea, pelvic pain, dyspareunia and infertility but a wide spectrum of physical symptoms may be involved.^{3,4} Women with endometriosis experience a decreased quality of life, and considerable loss of work productivity with associated costs have been identified.⁵⁻⁸ Unfortunately, endometriosis is characterized by a long interval between onset of symptoms and diagnosis.^{6,9-12} This diagnostic delay is partly due to factors related to the condition itself, like the variable symptom pattern, whether or not subfertility is present, and the fact that invasive diagnostic testing using laparoscopy has been the gold standard for diagnosis.^{9,13} Factors related to the health care organisation, the patients' help seeking behaviour and medical professionals' clinical strategies including referral habits have been proven of great importance as well.^{9,10,12,14} Research concerning endometriosis tends to focus on pathogenesis and medical strategies for diagnosis and treatment. However, recent studies on quality of care in endometriosis have shown increased interest in patient-centeredness.¹⁵⁻¹⁹ A systematic review on patient-centeredness of endometriosis care revealed that the most frequently reported improvement targets were 'timely diagnosis' and 'being believed and respected by medical professionals'.¹⁵ Although several studies have addressed these items^{9,10,12,20,21}, more in-depth information regarding delays in diagnosing endometriosis from the patients' perspective is needed to propose relevant interventions for improvement. The aim of this study was to identify strengths and weaknesses in the current diagnostic process of endometriosis from the patients' perspective, covering both their own help seeking behaviour and their experience with medical professionals on their journey towards the diagnosis of endometriosis.

Materials and Methods

Study design and data collection

Focus group interviews with women between 18 and 45 years old, who

have been diagnosed with endometriosis in the previous five years, have been conducted between March 2016 and March 2017. Participants were recruited by advertisements in social media, a national patient interest group and centres of expertise in endometriosis. The focus groups were organized throughout the country in conference rooms. Semi-structured interviews in groups of 2-6 participants were carried out rather than individual interviews because we expected that the interaction and sharing of experiences would generate more relevant information. The semi-structured approach allowed the participants to talk freely with structured guidance from the moderator, using an interview guide (appendix). The interview guide was based on the literature and experience of the authors, working in the fields of reproductive medicine, qualitative research, and implementation research. The topic guide was a dynamic document, on which topics were added when new items were identified during the interviews. In addition, each participant was asked to complete a short questionnaire to inform the researchers about their age, timeline in their diagnostic process and treatment history and personal suggestions for reducing the diagnostic delay. The group interviews were directed by a moderator (AN or MZ) with a backup for taking notes and process monitoring (MZ, LK or AN). We continued to organize focus group interviews until data saturation was achieved, which was defined as no additional information was gathered during subsequent focus group interviews, followed by one additional session for confirmation of data saturation. The participants received detailed information about the study design and signed an informed consent form prior to participating. Anonymity and confidentiality were ensured.

Data Analysis

The focus group sessions were audio recorded and fully transcribed. The qualitative research software package ATLAS-ti (v7.1) was used to assist in data analysis. We used the grounded theory methodology for data analysis.^{22,23} First, all transcripts were analysed by two of the authors (MZ and LK) independently by means of line by line open coding. After the individual coding of each transcript, quotation selection and codes were compared, and any discrepancies were resolved by discussion between the two researchers. Remaining differences of opinion were discussed with a third researcher (WN) until consensus was reached. This third researcher, a qualitative research specialist, checked samples of the transcripts for completeness of coding. After coding of all the transcripts, the full code list was analysed by the three coding authors and the researchers who moderated the focus

group interviews. In this session, the codes were grouped into categories and clustered into themes or domains. A summary of the analysis process is shown in figure 1. Study reporting was based on the Consolidated Criteria for Reporting Qualitative Health Research (COREQ).²⁴ We provided a quantification to indicate whether the results have been obtained from few (1-3), some (4-7), many (8-11) or most (12 or more) participants.

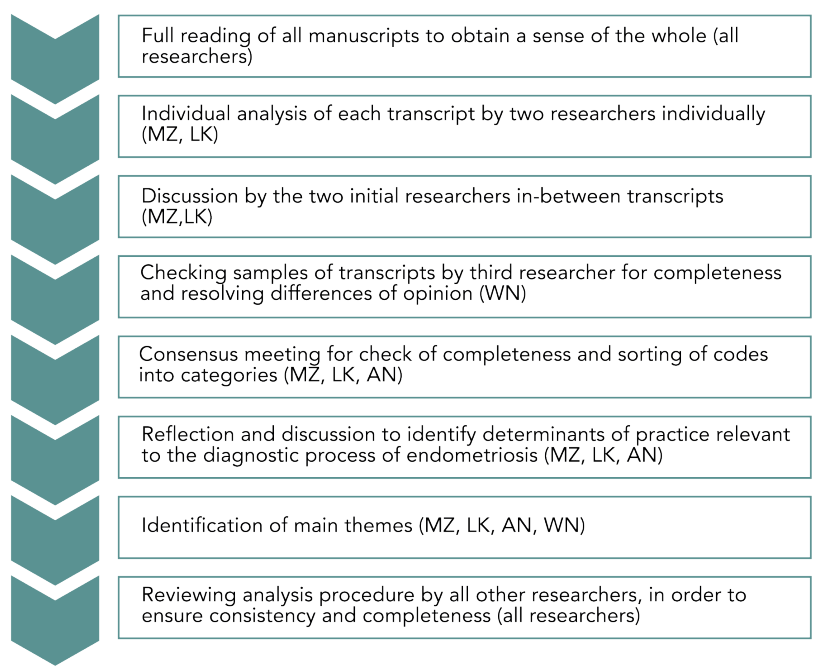


Figure 1. Summary of analysis process

Results

Six focus groups were conducted, in which in total 23 women participated. The duration of the focus groups was between 66 and 97 minutes. Mean age of participants was 33.9 years (range 29-45). Mean time from start of symptoms to diagnosis was 101.7 months or 8.5 years (range 0-216 months, SD 81.3 months). Most of the delay consisted of the time from onset of symptoms to first visit to the general practitioner (33 months) and time between first general practitioner visit and referral to a gynaecologist (61

months). Mean time since diagnosis was 3.8 years (range 0.5 – 9 years, SD 2.6 y). Two women were referred to the gynaecologist because of infertility, the other women had pelvic pain or other symptoms related to endometriosis. Twenty-one women (91.3%) reported a laparoscopy or MRI for confirming the diagnosis of endometriosis; the other two were diagnosed by gynaecologic examination including ultrasound imaging.

Analysis of the focus group interviews generated three main themes based on grouping of the most frequent codes and categories: 1) knowledge about normal menstruation and endometriosis in both the general population and medical professionals, 2) being believed and acknowledged by medical professionals, and 3) collaboration between health care providers including fast referral to a gynaecologist.

Knowledge about normal menstruation and about endometriosis

Many of the participating women reported problematic menstruation starting shortly after menarche or in adolescence. Help seeking behaviour was predominantly influenced by the interpretation of these complaints not only by the women themselves, but also by relatives and friends, in particular the mother. If participants had been told that their complaints were within a normal range, or that they were just unlucky to have pain, they started to dissimulate as well. When their mother, or significant others supported them in their feeling something was wrong, they were more likely to consult a doctor for their complaints. Some women mentioned that they suspected their mother had suffered from endometriosis as well, based on comparison of symptoms, without ever being diagnosed. These women were more frequently told that they just had to learn to live with the pain, or take pain medication.

“My mom told me it was normal and that I was just unlucky” [31y/o, delay 18 years]

A few women, who considered their complaints as normal, were directed to their general practitioner by a friend or relative who incidentally captured them during a painful period and told them it was not normal. Although many participants had compared their menstruation with their friends at young age, some also mentioned feelings of shame and perception of taboo.

“I was on a trip to Greece with a friend. I was lying on a chair like I was dying and she looked at me and said “what are you doing?” Then I told her

I felt like this every month and we started to talk about it [menstruation] and then I realised it was not normal. I was 30 years old at the time.”[M, 37 y/o, delay 14 years]

Being acknowledged by medical professionals

Almost all women with pelvic pain reported repeated consultations at the general practitioner's office for a diversity of symptoms which could later be attributed to endometriosis. Almost all of these women felt their symptoms were normalized or not taken seriously by the general practitioner. They perceived a lack of knowledge and skills concerning endometriosis resulting in insufficient acknowledgment in their call for help. Some were submitted to non-discriminatory tests or referred to the wrong medical specialist, or given numerous prescriptions for pain medication or contraceptive pills, often without the advice to take them continuously. Some of the participants never had a gynaecologic examination by their general practitioner despite repetitive consultations for abdominal pain or problematic menstruation. Five participants experienced restraint in further testing or referral because they were too young. Others were referred to the gynaecologist only after seeing a different general practitioner or during an emergency hospitalization. The gender of the general practitioner did not seem to affect the evaluation of symptoms according to the participants.

“My general practitioner never took it seriously because I didn’t want to get pregnant yet. I was 15 or 16 years old... I got prescribed different contraceptive pills all the time. I got referred when I was 20 years old and was trying to conceive.” [H, 29 y/o, delay 10 years]

There were participants with a fast referral to a gynaecologist as well. This was more likely if the patients reported specific complaints related to the menstruation, if they had tried to conceive for more than one year, if the women suggested endometriosis themselves or if they persisted in requesting referral.

“It was left in the middle for a while by the general practitioner. At some point I demanded a referral to a gynaecologist. My general practitioner thought it was ridiculous en unnecessary. But I persisted and then he said fine let’s do it.” [M, 37 y/o, delay 14 years]

Collaboration between health care providers

For most women, diagnosis was confirmed shortly after referral to a gynaecologist. Some women had multiple gynaecologist consultations before (complete) diagnosis, and participants observed an inequality in knowledge and skills between gynaecologists. A few women were diagnosed with endometriosis, but the full extent of the disease, in particular deep endometriosis, was not recognized from the beginning because of incomplete examination. Several participants encountered medical specialists other than gynaecologists because of their complaints, and many of them experienced that other specialists did not consider a gynaecologic condition or there was insufficient communication and collaboration between specialists.

“I just wished an internal medicine specialist or a urologist would think of it more easily. You’d say they work in the same hospital, why don’t you just call the gynaecologist to ask if they have any idea what is going on.” [E, 30 y/o, delay 11 years]

Table 1. Interventions to reduce diagnostic delay as suggested by the participants

Suggested interventions to reduce diagnostic delay	Number of participants
Improve knowledge about normal menstruation and endometriosis, recognizing of symptoms by GPs	13
Taking symptoms seriously and acknowledgement	11
More publicity about menstruation and endometriosis in general	9
Improve knowledge in other medical specialists and collaboration	8
Faster referral to gynaecologists by GPs	6
Improve quality of physical examination	5
Faster referral to specialized gynaecologist	2
Multidisciplinary teams	1
Reduce waiting lists for centres of expertise in endometriosis	1
No fertility treatment until complete diagnosis	1
Improve knowledge in gynaecologists	1

Suggested interventions to reduce diagnostic delay

The participants were asked about their suggestions to reduce diagnostic delay in endometriosis. Suggested interventions are given in Table 1. The most important interventions according to the participants were directed at increasing awareness in the general population, and providing medical staff (in particular general practitioners) with sufficient knowledge and skills to interpret presented symptoms or clinical findings correctly. Again, being taken seriously and acknowledgement appeared of major importance.

Discussion

Main findings

This qualitative study has yielded rich and important information about the experiences of women with endometriosis in reaching a diagnosis. The most striking finding was that most of the participants felt they were not taken seriously after disclosure of their symptoms. This influences their bodily perception and self image, and may lead to delayed consultation and referral, especially if their mother or other loved ones do not acknowledge their symptoms correctly. Being taken seriously by the general practitioner was the most frequently used code to label citations from the transcripts, and the second most frequent suggestion for improvement by participants.

Although it was challenging to distinguish patterns or similarities given the unique and complex nature of the participants' social and medical histories, many women experienced comparable struggles in their journey towards diagnosis. We identified barriers and facilitators at three different levels: the women's personal level, knowledge and skills of medical professionals, in particular general practitioners, and the interaction between patients and their health care providers. With regard to the women's personal level, self-recognition and interference of significant others appeared crucial for seeking medical help. For young women, the opinion of their mother turned out to be of key importance for the appraisal of their symptoms. This is an important finding because it may determine time to first consultation. Factors influencing the shift from normalizing of symptoms to help seeking behaviour have been proposed by Manderson et al.²⁵ Of the four catalysts described in the latter study (intercession, social disruption, biographic disruption, and self-recognition), intercession and self-recognition were the most prevalent in our study population. Differentiating between normal and abnormal appeared equally difficult for general practitioners according to the

participants. Most of the diagnostic delay in our study consisted of the time between first visit to the general practitioner and referral to a gynaecologist, which is in line with previous studies.^{9,12} The general practitioner needs to either recognize the presented symptoms as pathological, or acknowledge the significant impact of symptoms on the patient's life and thereby justify referral for further diagnostic tests.

Diagnostic delay was estimated at 8.5 years in this study, which is comparable with the existing international literature.^{9-12,26} In the Netherlands, the general practitioner has a strong position with regard to access to medical care, acting as a gatekeeper for medical specialist care. Other countries, including those in which specialist care is freely accessible, show a similar diagnostic delay.^{9,10,26,27} We suggest that the first medical professional consulted is the medical professional encountering the problem of differentiating between 'normal' menstrual complaints and signs or symptoms suggestive of endometriosis. Failure of this process may lead to misdiagnosis and delayed diagnostic tests or treatment.

Strengths and limitations

The importance of findings derived from qualitative research has been increasingly appreciated.^{22,28} However, careful consideration on study methodology is of great importance in order to secure study validity.^{24,29,30} To extract the most relevant information from the transcripts and preserve objectivity, we conducted a data-based analysis style by two independent researchers, and all steps of data analysis were discussed with several members of the research team. A wide diversity of aspects relevant to the diagnostic process were discussed in the focus groups, including women's own appraisal of symptoms, key elements in seeking medical help, and experience with medical professionals, both in primary and secondary care. Some of the participants were treated at the clinic in which one of the researchers was employed. They were informed in advance, encouraged to speak freely, and ensured that their contribution to the discussion would not influence their treatment in any way. These focus groups were moderated by a researcher not employed in the particular clinic if known in advance.

Interpretation

Diagnostic delay in endometriosis has been subject of several studies in the past decades. Even though many contributing factors have been described, the diagnostic delay does not seem to diminish. When asked

about their opinion about interventions to reduce the delay, the participants in our study mainly suggested improvements in knowledge and awareness and being taken seriously by medical professionals. They did not mention increasing efforts to expand scientific and medical knowledge, or focus on new diagnostic tests, but stressed the importance of being acknowledged in their symptoms and worries. Although the importance of developing an accurate non-invasive diagnostic test for endometriosis is obvious, in the meanwhile, it may be time to focus more on the clinical and personal aspects of reaching a diagnosis. Several studies suggested a switch from surgical to clinical diagnosis of endometriosis³¹⁻³³, a strategy that may reduce time between start of symptoms and adequate treatment even in the absence of a definite diagnosis. Focussing more on the person instead of the lesion creates opportunities for general practitioners to be more confident in their own diagnostic skills, and start empiric treatment in a timely matter. Adequate education to provide general practitioners with more knowledge about specific signs, symptoms and clinical findings possibly related to endometriosis and indications for referral is warranted to increase awareness on the condition and ensure specialist care when needed. Implementing this strategy may decrease reluctance in general practitioners for referral because of fear of inappropriate invasive testing as seen in one of our previous studies.³⁴ It is of great importance to make sure that when empiric treatment is started, the presumed diagnosis of endometriosis is communicated with the patient, a standardized therapeutic algorithm is followed in which hormonal therapy is given continuously instead of intermittently, and short term evaluation of the intervention is effectuated. In case of treatment failure or infertility, referral to a gynaecologist for specialist care (including expert medical treatment, advanced imaging, diagnostic or therapeutic laparoscopy and artificial reproductive techniques) is warranted. The development of a guideline, which is suitable for both general practitioners and gynaecologists or other medical specialists who encounter women in their reproductive life span with abdominal complaints, may support the feasibility of such a strategy. In addition, increasing awareness in the general population, in particular adolescent girls and women is of major importance to reduce patients' delay. Efforts have been made to identify the gaps in knowledge about endometriosis and preferences for information transmission in young women,³⁵ and several countries including the United States and Australia have developed outreach programs to expand knowledge in adolescents.³⁶ The Dutch patient interest group on endometriosis recently reported on a possible increase in awareness on endometriosis in women, resulting in a

reduction in time between onset of symptoms and seeking medical help.³⁷ These are important steps in reducing diagnostic delay in endometriosis.

Conclusion

In conclusion, the present study has shown that the diagnostic process in endometriosis is hampered by late presentation of symptoms to a medical professional, inadequate appraisal of symptoms and the interaction between patients and medical professionals. Women with endometriosis prompt their physicians to take them seriously. Efforts should be made to increase awareness in the general population, and to provide medical staff with sufficient knowledge and skills to adequately acknowledge presented symptoms or clinical findings and initiate appropriate actions.

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Disclosure of interests

The authors have no conflicts of interest. Funding: none

Contribution to authorship

MZ, DB, AN and WN contributed to the design of this study. AN and MZ hosted the focus group sessions. LK, MZ and WN analyzed the data, and all the other authors contributed to the interpretation of the data. MZ drafted the manuscript and AN, DB and WN made substantial contributions to it. All the authors critically revised the manuscript and approved the version to be published.

Details of ethical approval

The study protocol was evaluated by the Radboud University Medical Centre research ethics committee and did not require full institutional review board approval (Reference number 2016-2629)

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Appendix

Interview guide focus groups

Participants' opinion about factors related to the diagnostic delay

- When to consult a medical professional
- Involvement of friends, relatives and significant others
- Use of over the counter analgesics
- Effect of medical treatment initiated by general practitioner
- Knowledge of general practitioner concerning endometriosis
- Differentiating between normal and abnormal menstrual complaints
- Physical examination by general practitioner
- Use of additional diagnostic testing
- Time between first presentation to general practitioner and referral to secondary care (barriers and facilitators)
- Referral directly to gynaecologist or other medical specialist
- Time between referral to gynaecologist and diagnosis (barriers and facilitators)
- Subfertility
- Absence from school or work due to menstrual complaints
- Interaction between patient and medical professional, continuity of care

Participants' opinion about which factors are most important in endometriosis care, for instance (but not restricted to)

- Available (online) information about endometriosis
- Being taken seriously
- Continuity of medical care (same doctor)
- Timely start of empiric treatment
- Information given by medical professional
- Fast referral
- Referral to tertiary care (possible pros and cons)
- Knowledge about endometriosis in general practitioners (both related to the diagnostic procedure and support after diagnosis)
- Continuation of care by general practitioner after diagnosis and initiation of treatment by gynaecologist

Abstract

Endometriosis is the most common benign gynaecological disorder. The general practitioner (GP) plays an important role in identifying women at early stages of the disease. This study was conducted to acquire information about awareness and knowledge of endometriosis among Dutch GPs, and clinical strategies taken. A total of 101 GPs completed a questionnaire either by email or at a local education meeting. The GPs annually encounter 2.8 women they suspect of having endometriosis. The estimated time to diagnosis was 65.7 months (39.1 months patient delay and 26.6 months doctors delay); 56.7% of GPs primarily refer to a gynaecologist for consultation or diagnostic tests. The GPs answered on average 16.6 out of 28 knowledge questions correctly. Seventy-six out of 87 GPs stated that they needed further education. The results of this study indicate that if a GP considers endometriosis as a diagnosis, adequate action is undertaken. As only limited numbers of women with endometriosis are encountered in their practice, GPs do not recognize immediately the symptoms that may be caused by endometriosis, leading to diagnostic delay. Our findings may help to set up teaching programs and awareness strategies for first-line medical professionals to enhance timely diagnosis and treatment of endometriosis.

Introduction

Endometriosis is defined as the presence of functioning endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction.¹ It is a progressive condition affecting women in their reproductive life span. Endometriosis is the most common benign gynaecological disorder, with a reported prevalence of 2–10%, although it is difficult to estimate because laparoscopic visualization, histology, magnetic resonance imaging, or both, are required for definite diagnosis.^{2,3} In addition, many women experience only mild symptoms or respond well to treatment and do not receive a full diagnostic work-up.

As endometriosis is a progressive disease, which in many patients deteriorates over time, timely diagnosis and treatment are of major importance. The clinical presentation can be highly variable. Classic symptoms of endometriosis include dysmenorrhea, cyclic pelvic pain and dyspareunia. A wide variety of symptoms, however, may be presented, with many of them highly prevalent among young women, non-specific and overlapping with other conditions. This leads to difficulties in identifying those at risk for endometriosis, resulting in many women receiving either delayed or suboptimal care.^{4,5} A diagnostic delay of up to 10.7 years has been reported, and reflects both a delay in the patient attending primary care and a delay by the GP in reaching a diagnosis.⁶⁻⁹

General practitioners (GPs) and other first-line medical professionals play a pivotal role in identifying patients at an early stage of the disease. To be able to interpret the often cyclic and sometimes aspecific symptoms presented by these women correctly, awareness and knowledge of endometriosis is of major importance. The aim of this study was to explore the level of knowledge of endometriosis among GPs in the Netherlands and to evaluate their diagnostic and treatment strategies. The information gathered in this study will be used to formulate strategies to increase awareness of endometriosis among first-line medical professionals and to develop skills to reduce diagnostic delay.

Materials and methods

Questionnaire

A 51-item questionnaire was developed by AN in cooperation with local GPs, and was tested in a pilot study among 10 GPs (Appendix). Ten questions

related to the GPs' working practice, e.g. GPs' experience, and number of patients with complaints suggestive of endometriosis according to the GP. Twenty-eight questions tested the actual knowledge of endometriosis, six questions explored diagnostic and treatment strategies and six questions related to GPs' self assessment of their knowledge of endometriosis and need for education. The remaining questions were miscellaneous. The knowledge questions were multiple choice, and the strategy questions were both open-ended and multiple choice. Answers to the open-ended questions were categorized by MZ. To compose the categories, the answers most alike were clustered. Correction for guessing was applied.¹⁰ The final score on knowledge was applied only if at least 90% of questions were completed (26 or more). The questionnaire could not be validated because of the informative nature of the study and because no comparable studies were undertaken previously. The diagnostic delay represents the time from start of symptoms until diagnosis and comprises the time until first medical consultation at the GP office (patient delay) and the time from first GP consultation to diagnosis. In this study, the diagnostic delay reflects the GP's interpretation of these time intervals.

Data collection

The study population consisted of GPs located in practices in the region of Arnhem, the Netherlands. GPs were recruited at the beginning of the annual education meeting on gynaecology for GPs at the Rijnstate Hospital in Arnhem, or by email. This referral centre is specialized in the diagnosis and multidisciplinary treatment of endometriosis and is recommended by the Dutch Endometriosis Society, the endometriosis patient interest group. For GPs who answered the questionnaire on both occasions, only the answers given on the first occasion (at the start of the education meeting) were taken into account. This study was considered exempt from institutional review board or ethics committee approval because no individual patient data are involved as indicated by the Central Committee on Research Involving Human Subjects, The Hague.

Analysis

Statistical analysis was carried out using IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY, USA). Descriptives, T-Test and Pearson Correlation were used for analysis. Data are presented as mean with standard deviation unless stated otherwise. $P < 0.05$ was considered statistically significant.

Results

All of the 60 GPs at the education meeting completed the questionnaire. A total of 233 GPs were addressed by email, of which 53 responded (22.7%). In total, 101 GPs completed 113 questionnaires. Twelve GPs returned the questionnaire on both occasions, so their second questionnaire was not taken into account. In total, 101 questionnaires remained for analysis. Of these, 87 GPs answered at least 26 knowledge questions, and their scores were included for analysis (see Table 1 for baseline characteristics). The GPs encounter on average 2.8 ± 2.5 (range 0–20) women per year who they suspect of having endometriosis and 2.1 ± 3.1 (range 0–20) women who think they have endometriosis themselves. According to the GPs, when women come up with endometriosis as a possible explanation for their symptoms, most of them base this presumption on information gained on the internet (Figure 1).

Table 1. Baseline characteristics

Sex n (%)	
Male	29 (28.7%)
Female	57 (56.4%)
Unknown	15 (14.9%)
Full Time Equivalent (FTE)	0.70 ± 0.19
Practice experience (years)	14.2 ± 9.7

Results are indicated as mean \pm SD

GPs estimated the time from start of symptoms to first presentation to the GP to be 39.1 months (± 35.6), whereas time from first presentation at the GP until diagnosis is estimated at 26.6 months (± 33.1). The GPs consider cyclic symptoms and severe dysmenorrhea as typical complaints to trigger their awareness of endometriosis, but abdominal pain, abnormal bleeding pattern, aspecific abdominal complaints, cyclic urinary or defecation symptoms, dyspareunia and subfertility were also mentioned (Figure 2). When the GP suspected endometriosis, 12 (12.4%) referred for diagnostic tests, 30 (30.9%) started treatment (analgesics, oral contraceptives or IUD), 43 (44.3%) referred to a gynaecologist, five (5.2%) awaited the natural course for some time, one (1.0 %) gave lifestyle advice and six (6.2%) had other medical strategies.

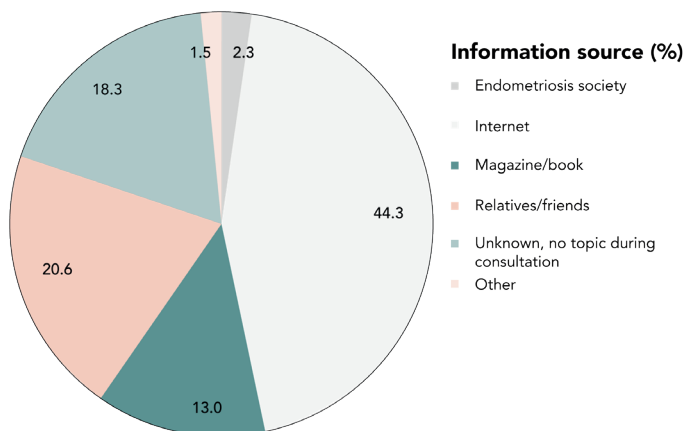


Figure 1. Information source for women who suspect themselves of having endometriosis.

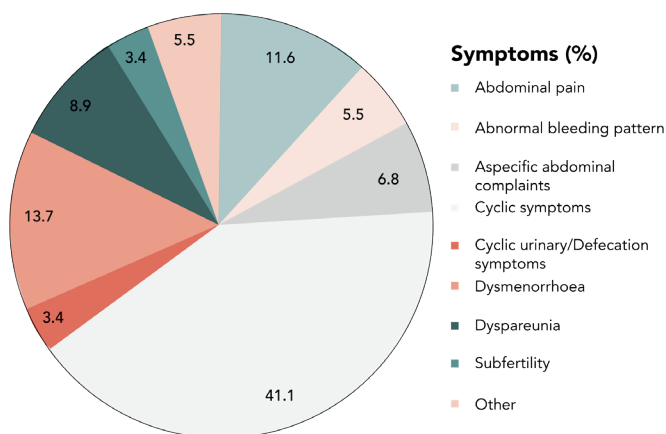


Figure 2. Symptoms that trigger the general practitioner to suspect endometriosis.

Of the 28 knowledge questions, the GPs answered on average 16.6 ± 2.4 (range 11–22) questions correctly (59.3%). The mean score after correction for guessing was 12.9 ± 3.4 or 46.1% (range 4–21, highest possible score 28) (Figure 3). The knowledge questions were divided into two categories: 10 questions about factual knowledge, e.g. pathophysiology or costs, and 18

questions concerning clinical insight, e.g., symptoms and treatment options. The GPs scored on average 4.0 points (40%) on factual knowledge and 8.9 points (49.4%) on clinical insight. The male GPs worked on average more hours a week (0.84 versus 0.63 full time equivalent; $P < 0.01$) and had more years of working experience (18.8 versus 11.7; $P 0.04$) compared with the female GPs. No significant differences were found in mean score (male 11.7 versus female 12.0) or number of correctly answered questions (male 16.6 versus female 16.6) between sexes. No correlation was found between the knowledge scores and number of patients with suspected endometriosis per year, or with patient exposition (weekly working hours and years of experience). Seventy six out of 87 GPs stated that they felt a need for education (14 GPs did not answer this question).

Discussion

This is the first study to explore the knowledge and diagnostic and clinical strategies of GPs to diagnose and treat endometriosis in The Netherlands. The results of the questionnaire help to clarify factors influencing diagnostic and treatment delay. It represents the opinion of GPs, in contrast to many other studies, which often have the patient or gynaecologist as information source. In our opinion, the information gathered in this study can help to formulate strategies to increase awareness of endometriosis among first line medical professionals, to develop skills to reduce diagnostic delay and ultimately to improve management of women affected by endometriosis. The GPs in our study estimate the total diagnostic delay at 65.7 months or 5.5 years: 39.1 months from start of symptoms to first presentation and 26.6 months from first presentation to diagnosis. According to previous studies, the diagnostic delay in other European countries varies from 4 to 10 years.^{6,8,9}

These numbers are difficult to compare because of differences in healthcare organizations and funding between countries, factors proven to influence time to diagnosis.⁹ Also, most studies use data obtained from the patient rather than from the GP. A patient based study in the same region we have undertaken showed a total diagnostic delay of 89 months, most of which reflected GP delay.¹¹ The difference in GP delay between the patient and GP-based questionnaire is 31.6%; however, these numbers are still within the lower range compared with other European countries. The high rate of referral for diagnostic tests or consultation in our study group (in total 56.7%) may indicate the GPs feel an urge for specialist confirmation of the diagnosis

before starting treatment. Moreover, it might also reflect bias as the GPs know the questionnaire was initiated by gynaecologists.

When asked about specific signs and symptoms suggestive of endometriosis, the GPs refer to a broad spectrum of complaints (Figure 2). Most GPs mention cyclic symptoms and dysmenorrhea as the main trigger for their suspicion. These are generally regarded as classic endometriosis symptoms. This indicates that GPs suspect endometriosis mainly based on the correct symptoms. If endometriosis is suspected, adequate actions including pain relief, hormonal treatment or referral to a gynaecologist are undertaken by most GPs.

The finding that, according to GPs, they encounter 2.8 patients with endometriosis in their practice a year indicates that the first diagnostic impression at presentation of symptoms is not aimed at endometriosis. The prevalence of endometriosis is estimated at 2–10%; the exact incidence is unknown. Each of the GPs in the study is expected to encounter between 7.4 and 36.8 women with endometriosis a year based on the average practice population of women aged 15–50 years (23.3% of total population, 2258 patients for fulltime practice) corrected for the average full time equivalent of 0.7.^{12,13} The results of this study show that many women who present with symptoms of endometriosis are not recognized as such by their GP. This leads to an unnecessary delay in diagnosis and treatment.

The present study has some limitations. First, the GPs who completed the questionnaire represent only a part of the total population of GPs in the region, which may lead to bias. There is a manifest difference in response rate between the GPs at the education meeting and those who were recruited by email. The GPs at the education meeting may have completed the questionnaire as an act of courtesy to the organizers of the meeting. The GPs who completed the questionnaire by email may have had an above average interest in gynaecological pathology. We did not explore characteristics of non-responding GPs; however, the demographics of the responding GPs by means of age, sex and years of working experience show a common pattern. Furthermore, some of the questions relate to GPs' own perception of information; for example the number of encountered endometriosis patients or the women's own appreciation of complaints or source of information. This may lead to bias as these issues are difficult to recall.

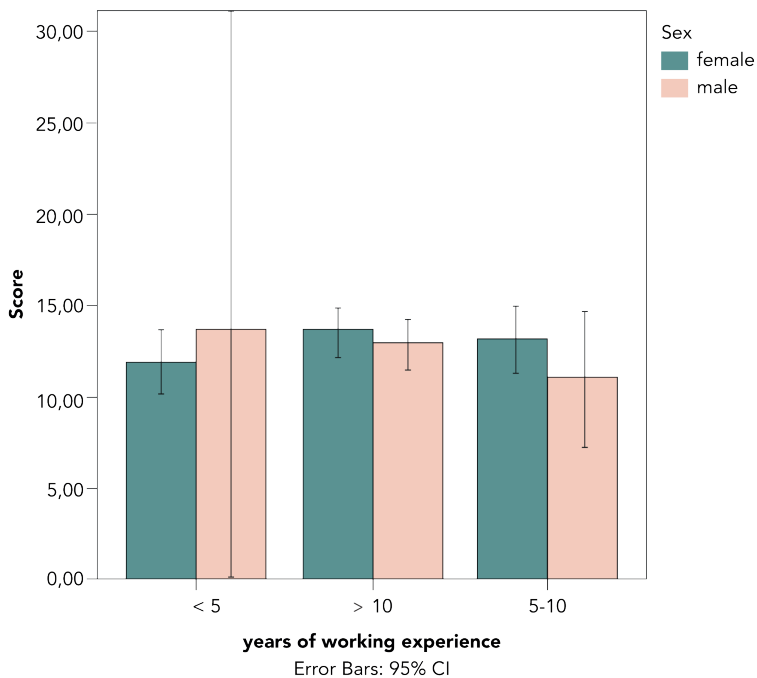


Figure 3. GP scores on knowledge questions.

The scores after correction for guessing are displayed separately for male (green bars) and female (blue bars) general practitioners for three categories of working experience.

Education of first line-medical professionals about diagnostic strategies, as well as pathophysiology and (empirical) treatment options may lead to a reduction in diagnostic delay. Recent developments in primary care organizations, such as the emergence of specialized GPs and advanced practice nurses, could lead to a more focused care for young women and should be encouraged. As indicated by the extensive patient delay mentioned in all studies, patient education is also of great importance. According to the GPs in our study, women who suspect endometriosis themselves obtain their information mainly on the internet (Figure 1). This may be an important target for providing adolescent girls and women with information about normal menstruation and when to seek medical help. This may encourage them to contact their healthcare provider in an early stage of disease and

therefore reduce the likelihood of advanced stages of disease and infertility. In conclusion, the present study has yielded new and important information about knowledge and diagnostic and clinical strategies for endometriosis. This information will be used in the development of future education programs for both first-line healthcare providers and young women to increase awareness about endometriosis.

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Appendix

Questionnaire Knowledge and treatment strategies on endometriosis

- 1. How many women do you on average see each year in whom you suspect endometriosis?
- 2. How many women do you on average see each year who think they have endometriosis themselves?
- 3. Do you know the average time between the start of symptoms and first presentation to the general practitioner in The Netherlands?
 - o Within 3 months
 - o 3 to 6 months
 - o 6 to 12 months
 - o 1 to 2 years
 - o 2 to 5 years
 - o 5 to 10 years
 - o More than 10 years
 - o I don't know
 - o Other, specify:
- 4. When women suspect themselves of having endometriosis, on what information do they base their presumption? (multiple answers possible)
 - o After contact with the Dutch Endometriosis Society, for example by visiting their website
 - o Internet (other than Dutch Endometriosis Society website)
 - o From magazine/book/brochure
 - o By contacting relatives/friends
 - o Unknown, this is usually no topic during the consultation
 - o Other, specify:.....
- 5. Which complaint(s) or symptom(s) trigger you most to consider endometriosis as a possible diagnosis?
.....
.....
.....

6. When you consider endometriosis as a possible explanation for the woman's complaints, what do you do first? (one answer)
 - o I await natural course
 - o I give the woman lifestyle advice, specify:
 - o I start medication, specify:
 - o I refer for diagnostic tests, specify:
 - o I refer to a second line medical professional (Continue at question 8)
 - o Other, specify:.....

7. For which amount of time do you await the result of this action? (Continue at question 9)
 - o Less than 3 months
 - o Three to 6 months
 - o Six to 12 months
 - o 1 to 2 years
 - o Other,specify:.....

8. Which second line medical professional do you refer to?
 - o Gynaecologist
 - o Urologist
 - o Surgeon
 - o Gastroenterologist
 - o Otherhealthcareprofessional,specify:.....

9. If your first treatment action did not work, which treatment is your second option? (If your first action does work, continue at question 15)
 - o I await natural course
 - o I give the woman lifestyle advice, specify:
 - o I start medication, specify:
 - o I refer for diagnostic tests, specify:
 - o I refer to a second line medical professional
(Continue at question 11)
 - o Other,specify:.....

10. For which amount of time do you await the result of this action? (Continue at question 12)
 - o Less than 3 months
 - o 3 to 6 months
 - o 6 to 12 months

- 1 to 2 years
 - Other,specify:.....
11. Which second line medical professional do you refer to?
- Gynaecologist
 - Urologist
 - Surgeon
 - Gastroenterologist
 - Otherhealthcareprofessional,specify:.....
12. If your second treatment action did not work, which treatment is your third option? (If your second action does work, continue at question 15)
- I await natural course
 - I give the woman lifestyle advice, specify:
 - I start medication, specify:
 - I refer for diagnostic tests, specify:
 - I refer to a second line medical professional
(Continue at question 14)
 - Other,specify:.....
13. For which amount of time do you await the result of this action?
(Continue at question 15)
- Less than 3 months
 - Three to 6 months
 - 6 to 12 months
 - 1 to 2 years
 - Other,specify:.....
14. Which second line medical professional do you refer to?
- Gynaecologist
 - Urologist
 - Surgeon
 - Gastroenterologist
 - Otherhealthcareprofessional,specify:.....

15. When you refer a woman because of endometriosis, which are the most important considerations for referral (which complaints/circumstances/experience)?

.....

.....

.....

16. Can you estimate on average the time between the first consultation at your office and your diagnosis of endometriosis?

- o Less than 3 months
- o 3 to 6 months
- o 6 to 12 months
- o 1 to 2 years
- o 2 to 5 years
- o 5 to 10 years
- o More than 10 years
- o Other,specify.....

17. Please indicate whether you agree or disagree with the following statements. If you are unsure, please choose "don't know".

(Correct answers are displayed in **bold**)

- | | | | |
|------|-----------------------------------------------------------------|----------------|--------------|
| 17.1 | Endometriosis can cause abdominal pain | | |
| | o True | o False | o Don't know |
| 17.2 | Endometriosis can cause cervical bleeding | | |
| | o True | o False | o Don't know |
| 17.3 | Endometriosis can cause dyspareunia | | |
| | o True | o False | o Don't know |
| 17.4 | Endometriosis can cause painful micturition | | |
| | o True | o False | o Don't know |
| 17.5 | Endometriosis can cause painful defecation | | |
| | o True | o False | o Don't know |
| 17.6 | Endometriosis can cause vaginal discharge | | |
| | o True | o False | o Don't know |
| 17.7 | Endometriosis can cause symptoms related to the menstrual cycle | | |
| | o True | o False | o Don't know |

- 17.8 Endometriosis associated symptoms are mainly caused by psychological issues
☐ True ☒ **False** ☐ Don't know
- 17.9 Pregnancy can aggravate endometriosis related symptoms
☐ True ☒ **False** ☐ Don't know
- 17.10 Postmenopausal women regularly experience symptoms caused by endometriosis
☐ True ☒ **False** ☐ Don't know
- 17.11 Endometriosis may be present without a woman being aware
☒ **True** ☐ False ☐ Don't know
- 17.12 Women with endometriosis are less likely to have successful IVF treatment as compared to women with tubal factor only
☒ **True** ☐ False ☐ Don't know
- 17.13 Analgesics are equally effective to oral contraceptives for treating endometriosis
☒ **True** ☐ False ☐ Don't know
- 17.14 Mirena IUD is a good treatment option for endometriosis
☒ **True** ☐ False ☐ Don't know
- 17.15 Tubal ligation is a good treatment option for endometriosis
☐ True ☒ **False** ☐ Don't know
- 17.16 Removing the ovaries is a good treatment option for endometriosis
☒ **True** ☐ False ☐ Don't know
- 17.17 Endometriosis can appear hereditary
☒ **True** ☐ False ☐ Don't know
- 17.18 Endometriosis can be related to endometrial cancer
☐ True ☒ **False** ☐ Don't know
- 17.19 Endometriosis can be related to ovarian cancer
☒ **True** ☐ False ☐ Don't know
- 17.20 Endometriosis appears mainly in the peritoneal cavity
☒ **True** ☐ False ☐ Don't know
- 17.21 Every month a day absent from school or work during menstruation indicates endometriosis until proven otherwise.
☒ **True** ☐ False ☐ Don't know
- 17.22 Endometriosis can induce permanent occupational disability
☒ **True** ☐ False ☐ Don't know

- 17.23 The costs of endometriosis to society are more comparable to those of migraine (relatively low costs) than to those of Crohn's Disease (relatively high costs)
- True
 - **False**
 - Don't know

18. In which percentage of women does endometriosis occur?
- **0-15%**
 - 16-30%
 - 31-45%
 - 46-60%
 - 61-80%
19. Endometriosis is probably caused by: (tick one answer)
- An irregular menstrual cycle
 - The presence of premalignant cells in the abdominal cavity
 - Psychological factors
 - The use of tampons
 - **The presence of endometrium outside the uterus**
 - Multiple sexual partners
 - Don't know
 - Other,specify:.....
20. At what age do women with endometriosis usually present their symptoms?
- Around menarche (10-15 years)
 - **During their reproductive life span (15-40)**
 - After their reproductive life span (after age 40)
 - Not related to a certain age, but related to their first sexual contacts
 - Don't know
 - Other,specify:.....
21. Which diagnostic test is considered the gold standard for confirming or declining the diagnosis endometriosis with certainty? (tick one answer)
- Vaginal ultrasound
 - Bimanual vaginal examination
 - Speculum exam
 - Magnetic Resonance Imaging (MRI)
 - **Diagnostic laparoscopy**
 - Don't know

22. Subfertility in endometriosis patients is usually caused by:
(tick one answer)
- ☐ Adhesions
 - ☐ The presence of old blood in the uterus
 - ☐ Not applicable, women with endometriosis are not commonly affected with fertility issues
23. How do you estimate your own knowledge on endometriosis?
(1 indicates uninformed, 10 indicates optimal knowledge)
24. Would you consider further education about endometriosis?
- ☐ Yes
 - ☐ No (continue at question 26)
25. Which kind of education would you prefer?
- ☐ Lecture
 - ☐ Receiving a book or brochure by mail
 - ☐ Individual education
 - ☐ Internet platform where you can gather information and deliberate with colleagues
 - ☐ Other,specify:.....
26. Are you satisfied with the quality of the information about endometriosis provided by the Dutch College of General Practitioners?
- ☐ Yes
 - ☐ No
 - ☐ Other,specify:.....
27. Are you familiar with the endometriosis guideline provided by the Dutch Society of Obstetrics and Gynaecology?
- ☐ Yes
 - ☐ No (please continue at the personal information section)
28. Do you use the Dutch Society of Obstetrics and Gynaecology guideline on endometriosis?
- ☐ Yes, during the consultation for gathering extra information
 - ☐ Yes, apart from the consultation, as study material
 - ☐ No

Personal Information (confidential)

Gender ○ Male ○ Female

Year of first registration as general practitioner:

Workload in Full-Time Equivalent:

Name:

Email address:

Comments:

Abstract

Background

Endometriosis is an invalidating gynaecological condition in women of reproductive age, and a frequent cause of infertility. Unfortunately, the condition is characterized by a long interval between onset of symptoms and diagnosis. General practitioners in the Netherlands are educated to provide basic gynaecological care and serve as gatekeepers for specialist medical care. Therefore, it is of great importance that they recognize signs and symptoms possibly caused by endometriosis in order to initiate adequate actions.

Objective

The main objective of this study was to identify barriers and facilitators to the timely diagnosis of endometriosis from the general practitioners' perspective.

Methods

Semi-structured focus group discussions with general practitioners were organized throughout the Netherlands. The participants were encouraged to brainstorm about their perspective on daily practice regarding endometriosis and suggestions for interventions in order to enable early diagnosis and treatment. Analysis was based on grounded theory methodology.

Results

Forty-three general practitioners participated in six focus groups. Analysis of the transcripts revealed relevant determinants of practice in four main themes: professionals' experience and competence, patient characteristics, guideline factors and professional collaboration. A lack of knowledge and awareness appeared to result in a low priority for establishing the diagnosis of endometriosis especially in young women. Infertility, patient engagement and a recent serious case or training facilitated referral.

Conclusion

Several factors in daily primary health care contribute to the diagnostic delay in endometriosis. Future interventions to reduce this delay may be aimed at increasing awareness by means of education, incorporating the subject into national clinical guidelines and improvements in interdisciplinary collaboration.

Background

Endometriosis is a common gynaecological disorder, with a reported prevalence of 2-10% in women of reproductive age ¹. It is defined as the presence of ectopic endometrial-like tissue which induces a chronic, inflammatory reaction ². The clinical presentation is highly variable, ranging from asymptomatic to invalidating pelvic pain and infertility. Besides classic symptoms such as severe dysmenorrhoea, cyclic pelvic pain and dyspareunia, nonspecific or vague symptoms such as periodic bloating, diarrhoea or constipation, dysuria and fatigue are often presented as well ^{3,4}. Some women respond well to symptomatic treatment by suppression of the menstrual cycle, however, a substantial number of women requires specialist consultation for diagnostics and treatment. Some patients experienced serious complaints that had not been addressed adequately for many years before eventually being diagnosed with endometriosis ^{5,6}. Diagnostic delay remains an issue of great concern, because it may lead to delayed treatment or suboptimal care with risk of infertility, organ damage, reduced quality of life and loss of work productivity or disability ^{7,8}. Previous studies have shown that the diagnostic delay in endometriosis is extensive and consists of several components related to both the patient and the doctor ^{6,7,9,10}. The general practitioner (GP) plays a pivotal role in identifying patients at an early stage of the disease. Awareness on endometriosis as a possible underlying cause of abdominal complaints, facilitates empiric treatment or early referral if needed. In the Netherlands, GP education is based on a structured schedule of theoretical teaching combined with exposure in clinical practice. GPs in training are educated on gynaecological subjects in a short theoretical module in which endometriosis is scarcely addressed. Midwives and non-medical personnel are not involved in the care of gynaecological problems.

To be able to develop targeted interventions aimed at reducing diagnostic delay, it is crucial to be aware of determinants of daily general practice which may impede or facilitate early recognition of endometriosis. The aim of this study is to explore the barriers and facilitators influencing time to diagnosis of endometriosis from the GPs' perspective.

Materials and Methods

Focus groups with general practitioners were performed between January 2016 and March 2017. Participants were recruited by contacting group

practices listed by the Dutch College of General Practitioners by email. Purposive sampling of group practices was performed based on geographical spread, on rural or urban area and on the employment of a GP specialized in urogynaecology. To be able to gain information from different levels of experience, we aimed to include a specialized GP in multiple focus groups and to organize one focus group exclusively with GPs in training. We continued to organize focus groups until data saturation was achieved, which was defined as no additional information was gathered during subsequent focus groups, followed by one additional focus group for confirmation of data saturation. Of the approximately 5.000 GP practices in the Netherlands, 29 were invited to participate in the study, based on the earlier-mentioned criteria. Only groups of collaborating GPs were invited, and focus groups took place in their own medical office. No incentives were provided for participation. We expected that the interaction and sharing of experiences in focus groups would generate more relevant information compared to individual interviews. The semi-structured approach allowed the participants to talk freely with structured guidance from the moderator, using a topic guide (supplementary material). The topic guide was based on the literature and experience of the authors (all female), working in the fields of reproductive medicine, primary care, qualitative research, and implementation research. It was a dynamic document, on which topics were added when new items were identified during the focus groups. All focus groups were directed by one experienced moderator (W.N.) with a backup for taking notes and process monitoring (M.Z.). The moderators were not personally or professionally related to the participants. The GPs signed an informed consent form before participating. Anonymity and confidentiality were ensured.

The focus groups were audio recorded and fully transcribed. The qualitative research software package ATLAS-ti (v7.1) was used to assist in data analysis. Grounded theory methodology was applied for data analysis, which was performed in tandem with the focus groups^{11,12}. A summary of the analysis process is shown in figure 1. Study reporting was based on the COREQ criteria¹³. We have provided a quantification to indicate whether the results have been obtained from few (1-3), some (4-10), many (11-21) or most (22 or more) participants.

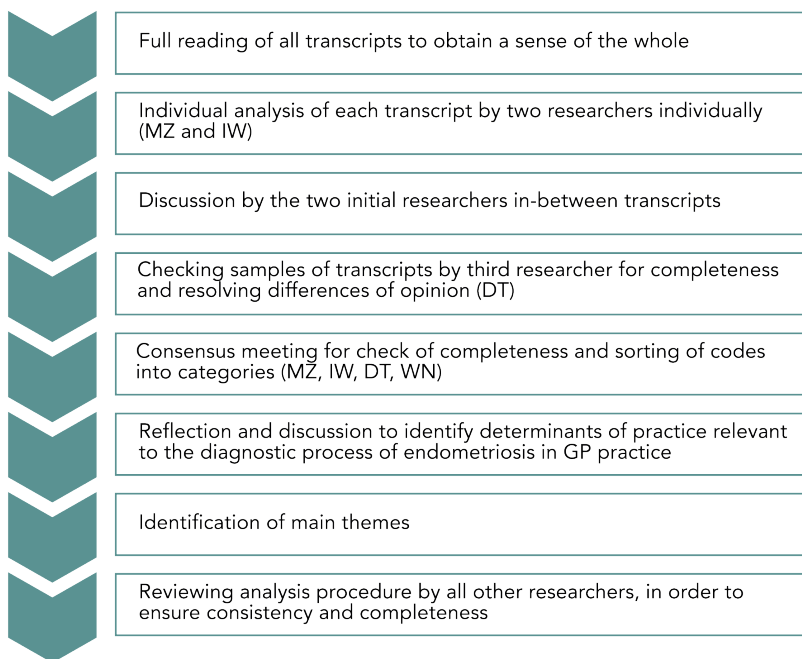


Figure 1. Procedure of content analysis

Results

GPs from 29 group practices were sent an invitation letter by email. Three of these were willing to participate themselves however, they failed to convince their associated colleagues to join and therefore rejected the invitation. One GP refused because endometriosis was covered in a local education program and 19 did not reply to the email. In total 43 GPs participated in six focus groups in both urban and rural areas throughout the country. One focus group was held exclusively with GPs in training (n=12), all from different practices. The other five focus groups were held with all GPs from one group practice each. Three of the participating GPs had completed an additional postgraduate training course for GPs specializing in urogynaecology; they participated in the focus group in their own practice. The duration of the focus groups was between 46 and 89 minutes. Descriptive data of participants are demonstrated in table 1. Analysis of the focus groups generated four main themes based on the grouping of the most frequent codes and categories, with regard to barriers and facilitators to a timely delay

in diagnosing endometriosis: professional experience and competence, patient characteristics, guideline factors and professional collaboration (table 2).

Table 1. Baseline characteristics of the GPs participating in the focus groups between January 2016 and March 2017

	FG 1	FG 2	FG 3	FG 4	FG 5	FG 6
Number of participants	8	8	7	3	12	5
Gender						
Male	2	4	1	1	1	1
Female	6	4	6	2	11	4
Specialty training in Women's Health	1	1	1	0	0	0
Type of practice						
Urban	0	8	1	3	1	3
Rural	8	0	6	0	0	1
Mixed/variable	0	0	0	0	11	1
Years in profession						
GP in training	1	0	0	0	11	2
< 5 years	1	1	3	1	0	1
5-20 years	4	5	3	1	0	1
> 20 years	2	2	1	1	1 [#]	1
Full time equivalent*						
Fulltime	0	0	0	0		3
Part-time	8	8	7	3		2

* GPs in training excluded

[#] Participating mentor of GPs in training

Professional experience and competence

Many participants reported limitations in knowledge about endometriosis. They realized that their training in endometriosis is limited, both in clinical traineeships and educational programs. A few GPs stated they do not know where to find easily accessible literature. Almost all GPs were unaware of the prevalence rate of endometriosis and considered it a rare condition.

"Well, you have to think of it in the first place. You have to know the condition before it even occurs to you. And if you don't think of it, you will not find the information you need." [FG2, GP1, male]

When GPs are consulted by women with dysmenorrhoea or other complaints

related to the menstrual cycle, they find it difficult to differentiate between physiological discomfort and pathological conditions like endometriosis. Moreover, consultations for abdominal complaints pose the difficulty of a wide differential diagnosis, which is mostly pointed to defecation and dietary patterns instead of a possible concurrence of complaints with the menstrual cycle.

"When I got the invitation [for the interview] I thought I hardly ever see endometriosis. But it's like when you buy a new car; all of a sudden you see a lot of them... Last week I got the results of a woman who had a laparoscopy because of endometriosis. A young adult who suffered from severe abdominal pain for many years. I thought she had a problem with her intestines, referred her to the gastroenterologist..."[FG4, GP2, female]

The quality of the history taking may define the nature and extent of the physical examination. This can lead to omitting a gynaecological examination if symptoms are not addressed correctly. A prior serious case in their practice or recent training appeared to facilitate awareness of endometriosis. Although some of the respondents were familiar with typical signs of endometriosis in basic gynaecological examinations, like the characteristic blue nodules in the posterior fornix, most GPs stated they consider their own knowledge and skills insufficient for diagnosing endometriosis.

"If you are more aware of the condition you can ask more detailed questions, and then you can have a suspicion..."[FG2, GP1, male]

Even when the GPs consider endometriosis, referral for further diagnostics is not always beneficial in their opinion. The GPs felt that definite diagnosis may induce a burden of disease or "stigma" to some women. Especially for young or adolescent women, for whom the GPs considered a gynaecological examination too invasive given the low probability of a pathological condition in their opinion, the willingness to refer to a gynaecologist was low.

"Moderator: For example a young girl, 16 years old, who comes to your office with complaints about her menstruation, would you tell her, you consider endometriosis when you prescribe her the pill? GP3: I wouldn't even think of it. GP2: No, me neither. I would think it just bothers her more than others. Or she just wants the pill, that's fine. GP3: Or PMS. Just try taking the pill. I would never say to anyone 'well you might have endometriosis, try this'. GP2: No way..."[FG4, GP2, female and GP3, male]

Many of the participating GPs routinely prescribed the contraceptive pill in a cyclic manner instead of continuously. They were not aware of the possibility of organ damage like infertility or chronic pain syndromes resulting from late diagnosis and treatment, nor the advice to fully suppress menstruation by hormonal therapy in case of endometriosis.

"GP1: But if you think of it and you start the pill you aren't doing anything wrong. GP8: Well they will have menstruations even on the pill, but would it be better to take it continuously rather than the usual way? I actually don't know about that. Should you advise women with endometriosis to take the pill continuously? GP3: I don't know for sure..."[FG1, GP1, male; GP3, female, postgraduate training; GP8, male]

Patient characteristics

It appeared that several patient characteristics influenced clinical strategies. GPs were more reluctant in referring patients with dysmenorrhoea as compared to patients with infertility. The GPs were more willing to refer to a gynaecologist if family planning came up during the consultation. The suggestion that timely diagnosis and treatment of endometriosis may prevent future infertility increased their sense of urgency. One GP suggested that a note with considerations about possible endometriosis in the patient's file may be helpful as a reminder if the woman presents some years later with persisting complaints or desire for pregnancy.

Women who frequently visit the GP's office with a wide spectrum of complaints and who perceive a high burden of those complaints were more often considered as somatizing and less frequently referred.

The GPs were more willing to refer women who are assertive during the consultation as compared to more passive women. They were more likely to consider endometriosis in women who brought information they found on the internet to the consultation. GPs considered additional diagnostic testing or referral if their own treatment strategy was not successful. However, they noticed that many women do not return to their office when symptoms persist, which makes it more difficult to identify those with treatment failure.

"There was this lady who had a wide range of complaints, very diffuse. And to be honest, she came up with the diagnosis [endometriosis] herself. Actually, I didn't much agree with her. But then the gynaecologist did a laparoscopy and it appeared to be endometriosis after all."[FG2, GP2, male]

Table 2. Barriers and facilitators in the diagnostic process of endometriosis according to the GPs participating in the focus groups between January 2016 and March 2017

Barriers			
Low sense of urgency for timely diagnosis	Not returning to the GP when initiated treatment fails	Lack of GP guideline	Lack of understanding gynaecologists' diagnostic/ treatment options
Limited experience with endometriosis	Young women less likely considered for pathologic condition		Low frequency of reporting on endometriosis in correspondence letters
Limited knowledge and skills related to endometriosis			Lack of knowledge in other medical specialists
Insufficient training and literature			
Facilitators			
Reluctance for referral because lack of gain perceived	Faster referral in case of infertility		Reporting of endometriosis as incidental finding may increase awareness
Recent case or training enhances awareness	Patient engagement promotes referral		
	Non-Western European background more easily referred		

A few GPs stated that women with a different ethnic background were more likely to get a fast referral, because of communication difficulties, different presentation of pain and the assumption that these women more frequently expect or demand a referral.

"Well I think I refer migrants easily, because I find the conversation more difficult. Communication about pain, how to handle it or how to address it. I somatise more easily, faster referral. They always present their symptoms more dramatically as well, and maybe they value diagnostic tests more than others. " [FG4, GP3, male]

Guideline factors

The lack of a national guideline for GPs concerning endometriosis or abdominal pain was mentioned in five out of six focus groups. The participants suggested a clinical guideline, written in their own language and developed by and for both GPs and gynaecologists. This joint guideline should ideally provide the GPs with a summary of the most recent relevant literature as well as clear instructions about which therapy they can start themselves, when referral is advised and which actions may be undertaken by the gynaecologists.

"GP1: One thing I do miss is the fact that none of our GP guidelines mention endometriosis. GP2: While apparently it has a high prevalence... GP1: Exactly. " [FG3, GP1, female and GP2, female]

"Maybe a joint guideline would help. So you will have something to pull up when you think of it. It would provide you with considerations and advice regarding diagnostics and treatment. " [FG3, GP6, male]and advice regarding diagnostics and treatment. " [FG3, GP6, male]

Collaboration

The GPs unanimously preferred more collaboration with gynaecologists about indications and instructions for empirical or first-line treatment and timing of referral. In all six focus groups, the GPs stated that they were reluctant in referring patients for further diagnostic testing on endometriosis. They questioned the added value of establishing a definite diagnosis and fear the inappropriate use of invasive techniques, since the treatment regimens appeared the same to them whether the diagnosis was confirmed or not. The participants suggested that improvements in the quality of correspondence after a woman is referred may increase awareness of endometriosis and motivation for early referral. They stated that reporting on considerations about endometriosis by the gynaecologists may help in a better understanding and motivates them to consider endometriosis more easily in future consultations. Besides this, they advised gynaecologists and

other medical specialists to report on endometriosis as an incidental finding or secondary diagnosis, for instance when spots are visualized at laparoscopy for another indication or when diagnosed in the workup of infertility.

"I think it would help if we got a lot of correspondence letters from the fertility specialists in which endometriosis is mentioned as a secondary diagnosis. That would keep us alert about the condition."[FG2, GP6, female]

The GPs experienced that other medical specialists like urologists, surgeons or gastro-enterologists also have a lack of knowledge about endometriosis. They suggested improving knowledge in these specialists, as well as collaboration between gynaecologists and other medical specialists.

Discussion

This study has yielded rich information about barriers and facilitators in general practice regarding the diagnostic process of endometriosis.

The most important finding is the fact that symptoms that may be characteristic for endometriosis, are not easily recognized. Moreover, GPs appear to have a low sense of urgency about confirming the diagnosis of endometriosis even if they consider it as a possible explanation for these symptoms. The GPs are rather reluctant in referring women to a gynaecologist for further diagnostics on endometriosis, especially if these women are of young age. These barriers to a timely referral and diagnosis possibly result from limitations in knowledge and awareness amongst GPs. Facilitating factors are infertility as reason for the consultation, patient engagement, and a recent serious case or training. The GPs stated that improvement in collaboration with gynaecologists is necessary. For example; in developing a joint national clinical guideline, improvement in correspondence letters and additional training for GPs. This may enhance awareness on endometriosis, including understanding of the importance of adequate treatment and when referral for advanced diagnostic testing or specialist treatment is required.

The importance of findings derived from qualitative research has been increasingly appreciated ^{11,14}. However, careful consideration on study methodology is of great importance to secure study validity ^{13,15,16}. To extract all relevant information in an objective manner, we conducted a data-based analysis style by two independent researchers, and all steps of data analysis

were discussed with several members of the research team. The variety of the research team is one of the strengths of this study. Moreover, we selected participants with different levels of experience to obtain a complete set of barriers and facilitators. The setting of focus groups with all colleagues from a group practice reduced the likelihood of including only participants with a special interest in the matter and therefore underreporting of barriers in daily practice. Although less than 0.5% of GPs in the Netherlands completed a specialty training in women's health, we intended to include group practices with a contracted specialized GP to make sure different levels of experience and exposure were represented in the study population.

Some limitations of this study should be discussed. Selection bias may have occurred because of the sampling procedure. However, the involvement of all GPs from the participating group practices, the geographical spread and the variety in level of experience increases the generalizability of our findings. Nevertheless, countries with a different health care setting may bring about other barriers and facilitators to a timely diagnosis of endometriosis. Furthermore, the determinants identified in this study may not be comprehensive, and future research activities directed at the diagnostic process can complement our findings.

To date, studies reflecting the GPs' perspective on endometriosis care are scarce. There are some retrospective studies about the diagnostic process in general practice based on primary care records reporting similar findings with regard to the role of the GP in the diagnostic delay of endometriosis. One study extracted information from primary care records in the UK demonstrating that repeated consultations and negative diagnostic tests contributed to a median delay of 9.0 years between first consultation and diagnosis¹⁷. Another British study identified a predictive value of linking features of consecutive consultations over time to a subsequent diagnosis of endometriosis¹⁸. This finding may help in the development of diagnostic support systems in general practice. Prevalence rates concerning endometriosis differ according to the type of study population, with higher estimated prevalence rates seen in clinical studies as compared to community-based or database estimates^{1,3,18-21}. Although population-based studies may appear to reflect the actual prevalence rate in general practice, they are likely to be hampered by incomplete coding in medical records or databases and missed diagnosis in symptomatic women. It is important for GPs to be aware of the possibility of an underlying condition like endometriosis in consultations concerning abdominal pain, dysmenorrhoea or other symptoms related to

the menstrual cycle, preventing unnecessary medicalization at the same time. A clinical guideline, covering first-line diagnostic and treatment strategies for women with abdominal or menstrual symptoms, including indications for referral may be useful in daily practice.

Conclusion

The quality of the diagnostic process of endometriosis in GPs is hampered by a limitation in knowledge and awareness, the lack of appropriate guidelines and insufficient collaboration between GPs and gynaecologists. These factors contribute to an extensive diagnostic delay. The present study was designed to explore determinants of practice regarding the diagnostic process of endometriosis in GPs in the Netherlands using a qualitative approach. Our principal aim was to identify possible barriers and facilitators rather than quantifying their relative importance. We recommend future research directed at prioritizing the individual barriers and facilitators, to be able to develop a multifaceted intervention strategy aimed at reducing diagnostic delay in endometriosis.

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Conflict of interest:	None

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Appendix

Interview guide focus group meetings

Objective: To identify barriers and facilitators in the diagnostic process of endometriosis from the GPs point of view

1. Exploring clinical strategies

- Recognizing endometriosis
 - o Estimation of prevalence of endometriosis in own population
 - o Length of diagnostic delay of endometriosis and possible contributing factors
 - o Symptoms that trigger the GP to consider endometriosis
 - o Knowledge of possible symptoms suggestive of endometriosis and reasons for consultation at GPs office
 - o Experienced difficulties in recognizing women with possible endometriosis
- Diagnostics
 - o Do GPs perform physical examination in case of a suspicion of endometriosis? Which examinations are performed and when?
 - o Do all women with possible endometriosis need to be seen by a gynaecologist to confirm the diagnosis?
- Treatment
 - o Do GPs start treatment in case of possible endometriosis? If yes: which treatment? If no: why not?
 - o Should endometriosis be treated by general practitioners and to what extent?
- Referral
 - o When are women referred to a gynaecologist? Which symptoms, signs or findings?
 - o Which women should definitely be referred to a gynaecologist?
 - o How can it be ensured that the women who have an indication for referral are seen by a gynaecologist?
- Attitude:
 - o How do GPs feel about women with endometriosis? Are they any

- different from other women and if yes: in which way?
 - o How do GPs feel about absenteeism from school or work during menstruation?
 - o To what extent is the burden of menstrual complaints influenced by coping abilities?
- Expectations:
 - o Is there any room for improvement? Can GPs perform better in diagnostics or treatment? How can this be achieved?
 - o Are GPs willing to change their routine concerning endometriosis?
 - o Are there any suggestions for interventions to reduce diagnostic delay in endometriosis in general practice?
- 2. **Exploring possible interventions**
 - o Do GPs (in training) get sufficient education about endometriosis?
 - o Which resources for knowledge on endometriosis are available to GPs?
 - o Which literature is used by GPs? Is the available literature appropriate and accessible for GPs?
 - o Are GPs familiar with existing guidelines on endometriosis? How do GPs appreciate these? Are the guidelines appropriate for use in family care?
 - o Is there a need for a national guideline on endometriosis? Should this be written for GPs only or for both GPs and gynaecologists?
 - o Would GPs consider additional education concerning endometriosis if available? What would be the best way to organise this?
 - o What would be of help in improving awareness and timely recognition of women with symptoms suggestive of endometriosis? Are GPs experienced with the use of screening tools, decision aid or other interventions in other medical conditions?

Abstract

Research question

To evaluate implementation of the key recommendations of the European Society of Human Reproduction and Embryology (ESHRE) guidelines on endometriosis, and to assess factors influencing diagnostic delay of endometriosis from Dutch gynaecologists' point of view.

Design

Questionnaire study among gynaecologists from all hospitals in the Netherlands. The questionnaire consisted of 56 questions relating to implementation of the ESHRE guidelines, organization of endometriosis care and diagnostic delay.

Results

Gynaecologists from 67 out of 85 hospitals completed the questionnaire. A total of 99–100% of respondents agrees with, and 91–100% adheres to, the diagnosis-related recommendations in the guidelines. Diagnostic delay is estimated at 42 months. Main factors contributing to diagnostic delay according to gynaecologists are lack of knowledge and awareness of endometriosis in both patients and medical professionals, as well as limitations in diagnostics and late referral. Suggested interventions to reduce diagnostic delay are aimed at improving knowledge and awareness in both patients and medical professionals, as well as improving collaborations between medical professionals.

Conclusions

Overall familiarity with, and use of, the 2014 ESHRE guidelines among Dutch gynaecologists is high. Dutch gynaecologists agree with the recommendations relating to diagnosis and adhere to them closely. Diagnostic delay, however, is still considerable; therefore, efforts to reduce diagnostic delay of endometriosis should be aimed at improving knowledge and awareness in both patients and medical professionals, as well as improving collaboration.

Introduction

Diagnostic delay in endometriosis remains a problematic issue. The time from onset of symptoms to diagnosis is reported to take up to 12 years.¹⁻⁴ The cause of this diagnostic delay is multifactorial. A wide variety of clinical symptoms, combined with the lack of an accurate non-invasive diagnostic test imposes difficulties for clinicians. In general, diagnostic delay is longer for women who first experience symptoms at a young age and relatively short for those who present with subfertility.^{1, 5} Women with chronic pelvic pain and an eventual diagnosis of endometriosis get the largest number of other diagnoses rather than endometriosis and have the highest rates of referrals compared with other causes of chronic pelvic pain.⁶ A study from the United States demonstrated that 23.5% of the participants visited more than four physicians before they were eventually diagnosed with endometriosis.⁷ Not surprisingly, the time between first seeking medical care and diagnosis increased with the number of physicians seen.

The variability in reported diagnostic delay between different study populations throughout the world suggests that factors related to healthcare organisation may also be involved. Accessibility to medical specialists varies and is commonly regulated by the government. In general, countries with government-funded health care show a stronger position and gate-keeper role for General Practitioners (GPs), whereas medical specialists in countries with insurance-funded health care are often freely accessible.⁸⁻¹⁰ Countries with a government-funded health care and a strong gate-keeper profile for GPs like the United Kingdom, Spain and Italy show a diagnostic delay of 8 to 10 years.⁴ Interestingly, in countries with insurance-funded health care and free accessibility to medical specialists, like Germany and Austria, a diagnostic delay of 10.4 years has been reported.³ Diagnostic delay of endometriosis in The Netherlands is reported as 7.4 years.¹¹ The Dutch health care system is insurance-funded, but is characterised by a strong position of the General Practitioner. A referral from the General Practitioner is mandated for reimbursement of health care costs by the insurance companies, and free access to medical specialists is therefore limited.

Awareness of endometriosis amongst GPs is of major importance to ensure timely referral to the correct medical specialist.¹² However, as diagnostic delay appears equally long in countries where patients present their symptoms to a medical specialist directly, it seems delays occur at the gynaecologists'

level as well. Data on factors contributing to this part of the delay are still lacking and require further attention in order to improve care performance and reduce the delay in diagnosis. Endometriosis is diagnosed and treated in all gynaecologists' practices in The Netherlands. There are no designated levels of expertise as in some other countries.¹³ The Dutch Society of Obstetrics and Gynaecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie, NVOG) has adopted the ESHRE guideline 'Management of women with endometriosis'¹⁴ and assumes that all gynaecologists are aware of its content. The ESHRE guideline provides recommendations on how the diagnosis of endometriosis should be established, "in an attempt to improve the knowledge of gynaecologists and other clinicians, and to decrease the diagnostic delay and the subsequent impact on the quality of life of women with endometriosis".¹⁴ Currently, there are no studies regarding the implementation and clinical use of this ESHRE guideline. This study is undertaken to investigate agreement with and adherence to the ESHRE guideline "Management of women with endometriosis" and to assess factors influencing the diagnostic delay of endometriosis from the gynaecologist point of view.

Material and methods

Data collection

A nationwide cross-sectional questionnaire study was performed among all hospitals in The Netherlands. One gynaecologist involved in the care for women with endometriosis from every hospital was invited to complete the questionnaire. After consent, a digital questionnaire was sent between May and July 2016 (NETQ Healthcare BV, Utrecht, The Netherlands). Gynaecologists who gave consent to participate in this study but did not complete the questionnaire before the deadline received a reminder by email after one to two weeks and eventually an additional reminder by telephone.

Questionnaire

An expert panel, including specialists in reproductive medicine (DB), endometriosis (AN) and guideline implementation (WN) was composed for the development of the questionnaire. The questionnaire consisted of 56 questions, both multiple choice (n=38) and open ended (n=18), which addressed demographic variables relating to the organisation of care, collaboration between medical professionals, opinion about centralisation of endometriosis care, current endometriosis care and diagnostic delay. Current

care performance was assessed by the organisation of endometriosis care and implementation of the ESHRE guideline 'Management of women with endometriosis' (Dunselman et al., 2014). Organisational aspects included the number of newly diagnosed patients per year, whether these patients are seen by all gynaecologists or gynaecologists with a sub-specialisation, the presence of a multi-disciplinary team and the diagnostic and therapeutic options in the respondents' hospital. The implementation of the ESHRE guideline was assessed by asking the gynaecologists about their familiarity and agreement with and practical implementation of the key recommendations in this guideline.¹⁵ These 17 key recommendations reflected a representative selection of the complete 83 item guideline as indicated by a panel of patients and medical professionals, and covers all aspects of endometriosis care. This included recommendations about diagnosis (n=4), treatment of endometriosis-associated pain (n=6), treatment of endometriosis-associated infertility (n=4) and the three miscellaneous topics prevention, menopause and cancer risk (n=1 for each topic). The term "diagnosis" was not specified in the questionnaire, which means that a suspicion based on physical examination and/or imaging techniques like ultrasonography or MRI sufficed, rather than confirmed by laparoscopy.

Agreement and adherence were assessed using a 5 (for agreement) and 6 (for adherence) point Likert scale. The answers "totally agree" and "agree" were scored as agrees with, and the answers "always" and "mostly" were scored as adheres to the recommendation. The questionnaire did not include validated instruments because no comparable studies were undertaken previously.

Analysis

Data were analysed using the Statistical Package for the Social Science (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY). Answers to the open questions were categorised by MA and AN according to whether they related to the patient, GP or gynaecologist. Similar answers were grouped and labelled with an appropriate caption. For these questions more than one answer could be given, therefore the total number of answers was not always equal to the total number of respondents to the questions.

Ethical approval

The study protocol was evaluated by the Radboud University Medical Centre research ethics committee and is considered exempt from institutional review board approval (Reference number 2016-2629, dated June 22, 2016).

Results

Participants

All 95 hospitals in The Netherlands were contacted. Some of them turned out to have merged, or appeared to be different locations of the same hospital. The representative gynaecologists from the remaining 85 hospitals were invited to participate, of which 67 completed the questionnaire (response rate 79%). In five hospitals no gynaecologist was willing to participate, six gynaecologists started the questionnaire but did not complete it, and seven gynaecologists did not start to fill in the questionnaire despite earlier consent. The demographic characteristics are shown in Table 1.

Table 1. Demographic characteristics of respondents (n=67) and hospitals

Characteristics	
Age (y)	47 [41-54]*
Gender (n)	
Male	35 (52%)
Female	32 (48%)
Years of working experience as a gynaecologist	11 [6.5-20.5]*
Type of hospital (n)	
Academic medical centre	7
Teaching hospital	33
Community hospital	27
Size of practice(FTE gynaecologists)	8.1 [5.8-12]*
New diagnosed endometriosis cases per Year (n)	55 [30-110.5]* #
Endometriosis patients are seen by (n)	
All gynaecologists	32 (48%)
A single gynaecologist / team of limited number of gynaecologists	35 (52%)
Subspecialisation of gynaecologists treating endometriosis patients (%)	
Benign gynaecology	18
Reproductive	13
Benign and reproductive	17
Oncology	2
No subspecialisation	17

*Values are median [interquartile range]

missing: 7

Guideline adherence

Almost all respondents were familiar with the guideline 'Management of women with endometriosis' (n=65, 97%). The agreement with and adherence to the individual key recommendations are shown in Table 2.

The key recommendations in the diagnostic domain were overall well known and applied. Agreement with the recommendation 'Assess ureter, bladder and bowel involvement by additional imaging if there is a suspicion based on history or physical examination of deep endometriosis, in preparation for further management' was high; however, 15 gynaecologists (22%) do not consistently operate according to this recommendation.

Regarding the treatment of endometriosis-related pain, a high number of gynaecologists agreed with the following recommendations: 'Prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment' (82%), 'Surgically treat endometriosis when identified at laparoscopy, i.e. 'see and treat', as this is effective for reducing endometriosis-associated pain' (84%) and 'Refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context' (93%). However, fewer gynaecologists typically operate according to these recommendations (67%, 75% and 78% respectively).

The agreement on the recommendations for treatment of endometriosis-associated infertility appears to be quite high (84-96%) and most of the gynaecologists apply them in practice (84-93%).

In the miscellaneous topics, agreement was high on the recommendations 'Continue to treat women with a history of endometriosis after surgical menopause with combined estrogen/progestagen or tibolone, at least up to the age of natural menopause' (90%) and 'Fully inform and counsel women about any incidental finding of endometriosis' (88%), whereas these recommendations were less often applied (82% and 78% respectively). The last recommendation 'Inform women with endometriosis, requesting information on their risk of developing cancer that (i) there is no evidence that endometriosis causes cancer, (ii) there is no increase in overall incidence of cancer in women with endometriosis and (iii) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis' scored lower on both agreement (76%) and appliance in practice (52%).

Table 2. Familiarity, agreement and adherence to key recommendations

Recommendation	Familiar with	Agrees with	Adheres to
Consider the diagnosis of endometriosis in the presence of gynaecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue in the presence of any of the above	67 (100%)	66 (99%)	63 (94%)
Consider the diagnosis of endometriosis in women of reproductive age with non-gynaecological cyclical symptoms (dyschezia, dysuria, hematuria rectal bleeding and shoulder pain)	66 (99%)	66 (99%)	61 (91%)
Perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma	66 (99%)	67 (100%)	67 (100%)
Assess ureter, bladder and bowel involvement by additional imaging if there is a suspicion based on history or physical examination of deep endometriosis, in preparation for further management	65 (97%)	64 (96%)	52 (78%)
Counsel women with symptoms presumed to be due to endometriosis thoroughly, and empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens	66 (99%)	65 (97%)	59 (88%)
Prescribe hormonal treatment (hormonal contraceptives, progestagens, antiprogestagens or GnRH agonists) as one of the options, as it reduces endometriosis-associated pain	66 (99%)	66 (99%)	62 (93%)
Take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain	64 (96%)	64 (96%)	61 (91%)
Prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment	60 (90%)	55 (82%)	45 (67%)

table continues

Surgically treat endometriosis when identified at laparoscopy, i.e. 'see and treat', as this is effective for reducing endometriosis-associated pain	60 (90%)	56 (84%)	50 (75%)
Refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context	63 (94%)	62 (93%)	52 (78%)
Perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only in infertile women with AFS/ ASRM stage I/II endometriosis, to increase ongoing pregnancy rates	65 (97%)	60 (90%)	58 (87%)
Perform excision of the endometrioma capsule, instead of drainage and electro coagulation of the endometrioma wall in infertile women with ovarian endometrioma undergoing surgery, to increase spontaneous pregnancy rates	59 (88%)	56 (84%)	56 (84%)
Counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery	63 (94%)	64 (95%)	62 (93%)
Use assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed	64 (96%)	63 (94%)	61 (91%)
Continue to treat women with a history of endometriosis after surgical menopause with combined estrogen/progestagen or tibolone, at least up to the age of natural menopause	61 (91%)	60 (90%)	55 (82%)
Fully inform and counsel women about any incidental finding of endometriosis	57 (85%)	59 (88%)	52 (78%)
<i>table continues</i>			

Inform women with endometriosis, requesting information on their risk of developing cancer that (i) there is no evidence that endometriosis causes cancer, (ii) there is no increase in overall incidence of cancer in women with endometriosis and (iii) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis	50 (75%)	51 (76%)	35 (52%)
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Diagnostic delay

Participants estimated the median time period between the onset of symptoms and diagnosis to be 42 months. When asked about which period of delay would be acceptable, 65 out of 67 respondents (97%) indicated that a period of less than two years from start of symptoms and diagnosis should be aimed for, and over half of the respondents (n= 35), advocated a maximum delay of 3-6 months.

The respondents state that patients, GPs and gynaecologists all contribute to the diagnostic delay of endometriosis. The responses to the open ended questions regarding which factors impede timely diagnosis are shown in Table 3. Factors relevant for patients, GPs as well as gynaecologists are trivialisation of complaints, lack of knowledge about endometriosis and failure to recognise symptoms. Patient specific factors were vague presentation of symptoms and avoidance of healthcare. Late referral to a gynaecologist was identified as a GP specific factor. Misdiagnosis, incomplete history taking and/or incomplete physical examination and limitations in performing diagnostic tests were all identified as contributing factors in relation to gynaecologists and GPs. Misdiagnosis may be more common among GPs, whereas being restrictive in diagnostic testing was one of the most important factors among gynaecologists.

Interventions aimed at reducing diagnostic delay may be initiated by patients and health professionals (Table 4, open ended question). However, according to gynaecologists, organisations and institutions including the Dutch patient interest group (Endometriosis Society, ES), the Dutch Society of Obstetrics and Gynaecology (NVOG), the government, and the media, all may play a role in reducing the time to diagnosis. The respondents state that one of the most important actions for reducing diagnostic delay was increasing knowledge and awareness amongst all stakeholders, including young women, GPs and gynaecologists.

Table 3. Factors contributing to the diagnostic delay of endometriosis according to subjects

Factor	Patient n (%)	GP n (%)	Gynaecologist n (%)
Trivializing of symptoms	36 (54%)	21 (31%)	6 (9%)
Lack of knowledge	28 (42%)	36 (54%)	16 (24%)
Failure to recognize	9 (13%)	23 (34%)	21 (31%)
Treatment without diagnosis	4 (6%)	10 (15%)	7 (10%)
Misdiagnosis	-	19 (28%)	4 (6%)
Limitation in history taking	-	2 (3%)	6 (9%)
Limitation in physical examination	-	3 (4%)	11 (16%)
Limitation in diagnostics	-	5 (7%)	16 (24%)
Vague presentation of symptoms	14 (21%)	-	-
Avoiding healthcare	13 (19%)	-	-
Healthcare shopping	2 (3%)	-	-
Late referral	-	6 (9%)	-
Restraint in the use of diagnostics	-	-	21 (31%)
No related factor	-	-	4 (6%)

According to the participants, patient delay may be reduced if symptomatic women were more assertive and visited their doctor more timely. To improve delays in relation to medical professionals, GPs and gynaecologists should avoid trivialisation and perform more accurate history taking and physical examination. Time taken for referral to a gynaecologist should be reduced. Gynaecologists were advised to collaborate more often and improve communication with GPs.

Participants suggested that the patient interest group should provide information to women in order to increase awareness of endometriosis. Providing information and education to GPs by the patient interest group was also suggested. The respondents state that besides providing information to patients and aiming to increase knowledge among gynaecologists, the NVOG may also advocate centralising endometriosis care (16%) and

promoting the implementation of the ESHRE guideline or even creating an improved version (13%).

Table 4. Suggested interventions to reduce diagnostic delay

Intervention	Patient n (%)	GP n (%)	Gynaecologist n (%)
Being more assertive	31 (46%)		
Increasing knowledge	22 (33%)		
Timely visit a GP	17 (25%)		
Recording of symptoms	7 (10%)		
Keeping knowledge up to date		33 (49%)	10 (15%)
Performing full history		13 (19%)	5 (7%)
Limit trivialization		9 (13%)	8 (12%)
Applying low threshold empirical treatment		5 (7%)	4 (6%)
Performing full physical examination		3 (4%)	11 (16%)
Applying low threshold diagnostics		2 (3%)	2 (3%)
Faster referral to gynaecologist		33 (49%)	
Providing information/ advise to patient		2 (3%)	
Cooperation with gynaecologist		2 (3%)	20 (30%)
Providing education			7 (10%)
No intervention	2 (3%)		4 (6%)

According to the respondents, the government may initiate a number of interventions including the provision of information to women (45%), and funding scientific research (10%). A majority of respondents (69%) state that the media has a role to play in decreasing time to diagnosis; by providing information to adolescent girls and women in order to increase awareness is mentioned as a possible intervention. However, a minority of the respondents (15%) were opposed to this because, in their opinion, reliable information in the media is scarce.

Organisation of care in the Netherlands

Multi-disciplinary teams were operative in 35 of the 67 participating hospitals (52%). The teams consist of gynaecologists collaborating with a surgeon (31/35), radiologist (27/35), urologist (26/35), gastroenterologist (12/35), pain specialist (13/35), and/or a psychologist (13/35). Less frequently other medical professionals were involved including dieticians (4/35), pelvic floor physiotherapist (4/35), sexologist (4/35), medical social worker (2/35) and/or continence or stoma nurse (2/35). Surgery for deep endometriosis was performed in 35 of the 67 hospitals (52%) and 30 out of these 35 hospitals (86%) had multi-disciplinary teams.

Collaboration

Most respondents state that they collaborated with other hospitals (n=62). Collaboration consists of regular contact by phone or email and referral. The majority refers patients (n=55), 29 hospitals receive patients referred from others. The main reasons for referrals are insufficient effect of an applied treatment (n=40), requiring surgery (n=42) and subfertility concerns (n=25), especially in women with deep endometriosis.

Centralisation

A majority of respondents (n=41, 61%) is in favour of centralisation because of the complexity of the disease, and to improve quality of care and to promote (interdisciplinary) cooperation. According to the gynaecologists, expert clinics could be established from regional collaborations in which a multidisciplinary approach, high volume in new patients and experiences with complex surgery, scientific research and level of patient satisfaction guiding the allocation of these clinics. Many of the respondents who oppose to centralisation state that less severe cases do not require centralized care.

Discussion

The ESHRE guideline 'Management of women with endometriosis' seems overall well known and applied by the respondents; 99-100% of participants in the study agrees with, and 91-100% adheres to the diagnosis-related recommendations in the ESHRE guideline. However, diagnostic delay is still a large concern in endometriosis in which a variety of factors may play a role. There are no comparable studies from other countries about adherence to the ESHRE guideline. This could provide interesting information on differences and possible opportunities for improvement.

The exact influence of guideline adherence on diagnostic delay is not known. It seems likely that knowledge of diagnosis-related items in the guideline may reduce diagnostic delay. However, evidence on the correlation between guideline adherence and diagnostic delay is lacking. Adopting clinical guidelines into routine daily practice requires interventions and effort at different levels. Analyses of barriers to changing practice have shown that obstacles can arise at the level of the individual professional, patient, health care team, health care organisation, or the wider environment. A good understanding of these barriers is very important.^{16,17} Moreover, it is likely that other factors are important as well, since the diagnostic delay is still extensive despite the good adherence to the diagnosis-related recommendations by our respondents. It would be interesting to study whether the ESHRE guideline is well known amongst GPs as well, since the doctors' delay is determined for a considerable part by the GPs.¹¹

To our knowledge, this is the first study to report on factors contributing to diagnostic delay of endometriosis from the gynaecologist's point of view. Although the respondents are well aware of the diagnostic delay and wish to reduce time to diagnosis, they underestimate the length of the delay by approximately one third. The same phenomenon is seen in Dutch GPs.¹² Main factors contributing to diagnostic delay according to the gynaecologists are a lack of knowledge and awareness of endometriosis in both patients and medical professionals, as well as limitations in diagnostics and late referral to a gynaecologist. This observation is in line with previous studies.^{1, 3, 4, 18} There are subtle differences in contributing factors between the different types of medical professionals. The contributing factors for GPs are mainly aimed at knowledge and recognition, as for gynaecologists the proper use of diagnostics seems an important issue as well. Proposed interventions to facilitate early diagnosis are in part directed at these factors and include promoting patient awareness and participation, increasing knowledge in medical professionals and facilitating timely referral to a gynaecologist. Furthermore, the respondents suggest an improvement in collaboration between medical professionals. Although most respondents state they already collaborate with other hospitals, this is still one of the most frequently mentioned facilitating factors for gynaecologists. Suggested interventions include promoting referral to expert gynaecologists, improving collaboration with other medical specialists, for example surgeons and gastroenterologists, and facilitating the centralisation of endometriosis care. This is an interesting finding, since the suggested improvements in collaboration do not match

observed causative factors for the delay, which mainly focus on improving knowledge and adequate use of diagnostics. They are however in line with the relatively low adherence to the guideline recommendations regarding the radiologic assessment of patients with a suspicion of deep endometriosis and referral of these patients to a centre of expertise which offers multidisciplinary treatment. Interestingly, the opinion of the respondents about centralisation seems contradictory as 61% of respondents were in favour of centralisation and 39% state they oppose to it. However, when asked about their motivation, those who claim to reject centralisation mainly point out that centralised care is not necessary for all patients, but only for women with severe endometriosis who may need complex surgery. This suggests that they may not be opposed to the concept of centralisation, but wish to preserve the opportunity to practice low-complex endometriosis care in all hospitals. A model with designated levels of expertise, as introduced in Belgium by D'Hooghe et al,¹³ may correspond to the suggestions regarding both directing endometriosis care according to the complexity of individual cases, as well as improving collaboration between gynaecologists in different hospitals and with other medical specialists. Another important observation was the advice to improve the collaboration between gynaecologists and GPs.

There are some limitations to this study. Although the response rate is high, only one gynaecologist from each hospital was invited to complete the questionnaire. Therefore, we may have missed relevant suggestions from other gynaecologists. Moreover, as our respondents are the gynaecologists most responsible for endometriosis care in their hospital, they may not be representative of the general-care gynaecologist. These gynaecologists with special interest in endometriosis are more likely to be familiar with the ESHRE guideline and have implemented it in their daily practice. The sample may be biased as those who are not familiar with the guideline, were probably less likely to respond. The questionnaire was not completed by any gynaecologist in 18 hospitals. The non-responding hospitals included all types of hospitals, such as academic, teaching and community hospitals. It should be noted that over estimation of guideline adherence by response bias is a well-known phenomenon. A review from Adams et al. has shown a median over-estimation of guideline adherence of 27% when self-reported measures are compared with objective measures.¹⁹ Another noteworthy point is the questionnaire was not validated because this is the first study to assess the opinion of gynaecologists on diagnostic delay and the use of the ESHRE guideline. Furthermore, we only quantitatively explored the guideline

adherence, as in-depth assessment of motivations for non-compliance would have taken too much time for the respondents, which might have led to a lower response rate. This could be addressed in future studies and may fine-tune implementation strategies.

In conclusion, the results of the current study indicate that the overall familiarity with and use of the 2014 ESHRE guideline 'Management of women with endometriosis' amongst Dutch gynaecologists is high. In particular, the recommendations concerning diagnosis are highly agreed and adhered to. As diagnostic delay is still considerable, efforts to reduce the diagnostic delay of endometriosis should be aimed at improving knowledge and awareness in both patients and medical professionals, as well as improving collaborations between gynaecologists and GPs, and other medical specialists, and above all, between gynaecologists from different hospitals throughout the country.

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Conflict of interest

None of the authors have any conflict of interest to declare

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Appendix

Questionnaire diagnostic delay and organization of endometriosis care

Background information

What is your age?

..... Years

What is your gender?

☐ Male

☐ Female

How many years are you currently employed as a gynaecologist?

..... Years

In which district did you complete your specialty training for obstetrics and gynaecology?

☐ Amsterdam VU

☐ Amsterdam AMC

☐ Leiden

☐ Rotterdam

☐ Groningen

☐ Utrecht

☐ Nijmegen

☐ Maastricht

☐ Other, please specify

In which hospital are you currently employed?

.....

How many gynaecologists are employed in your hospital?

.....

How many new patients with endometriosis are seen in your hospital each year?

.....

What is the format of consultations for endometriosis patients in your hospital?

- ☐ Women with (suspected) endometriosis are seen by all gynaecologists
- ☐ Women with (suspected) endometriosis are seen by a single gynaecologist/small team of gynaecologists
- ☐ My hospital does not treat women with (suspected) endometriosis

What is the subspecialisation of gynaecologists treating endometriosis patients?

- ☐ Benign gynaecology
- ☐ Reproductive medicine
- ☐ Other, please specify
- ☐ No subspecialisation

Endometriosis

Diagnostics

Which of the following tests are applied in your hospital to diagnose endometriosis? (you can select more than one answer)

- ☐ History
- ☐ Clinical examination (speculum, bimanual examination)
- ☐ Laboratory tests: CA-125
- ☐ Imaging: ultrasound
- ☐ Imaging: MRI
- ☐ Diagnostic laparoscopy

Please estimate the length of the “diagnostic delay” of endometriosis in the Netherlands (the time between onset of symptoms and diagnosis):

- ☐ Less than 3 months
- ☐ 3-6 months
- ☐ 6-12 months
- ☐ 1-2 years
- ☐ 2-5 years
- ☐ 5-10 years
- ☐ More than 10 years

Which length of the diagnostic delay would be acceptable in your opinion?

- ☐ Less than 3 months
- ☐ 3-6 months

- ☐ 1-2 years
- ☐ 2-5 years
- ☐ 5 -10 years
- ☐ More than 10 years

Which patient related factors contribute to the diagnostic delay of endometriosis in your opinion?

.....

.....

Which general practitioner related factors contribute to the diagnostic delay of endometriosis in your opinion?

.....

.....

Which gynaecologist related factors contribute to the diagnostic delay of endometriosis in your opinion?

.....

.....

Which other factors contribute to the diagnostic delay of endometriosis?

.....

.....

Which efforts can be made by the patient to reduce the diagnostic delay?

.....

.....

Which efforts can be made by the patient interest group to reduce the diagnostic delay?

.....

.....

Which efforts can be made by the general practitioner to reduce the diagnostic delay?

.....

.....

Which efforts can be made by the gynaecologist to reduce the diagnostic delay?

.....

.....

Which efforts can be made by the Dutch Society of Obstetrics and Gynaecology (NVOG) to reduce the diagnostic delay?

.....

.....

Which efforts can be made by the government to reduce the diagnostic delay?

.....

.....

Which efforts can be made by the media to reduce the diagnostic delay?

.....

.....

Can you think of any additional interventions to reduce the diagnostic delay?

.....

.....

Treatment

Which options for the treatment of endometriosis related pain are applied in your hospital? (you can select more than one answer)

- ☐ Analgesics
- ☐ Basic hormonal treatment (COC, progestagens)
- ☐ Advanced hormonal treatment (GnRH analogues)
- ☐ Operative
- ☐ Referral to another hospital
- ☐ These patients aren't treated in our hospital

Which options for the treatment of deep endometriosis are applied in your hospital? (you can select more than one answer)

- ☐ Analgesics
- ☐ Basic hormonal treatment (COC, progestagens)
- ☐ Advanced hormonal treatment (GnRH analogues)

- ☐ Operative
- ☐ Referral to another hospital
- ☐ These patients aren't treated in our hospital

Which options for the treatment of endometrioma are applied in your hospital? (you can select more than one answer)

- ☐ Analgesics
- ☐ Basic hormonal treatment (COC, progestagens)
- ☐ Advanced hormonal treatment (GnRH analogues)
- ☐ Operative
- ☐ Referral to another hospital
- ☐ These patients aren't treated in our hospital

Which treatment options are available in your hospital for patients with endometriosis who have a desire for pregnancy? (you can select more than one answer)

- ☐ Expectant management
- ☐ Operative
- ☐ Intrauterine insemination (IUI) combined with mild ovarian stimulation
- ☐ In vitro fertilisation (IVF)
- ☐ Referral to another hospital
- ☐ These patients aren't treated in our hospital

If operative treatment of women with endometriosis in your hospital, which types of endometriosis do you treat? (you can select more than one answer)

- ☐ Not applicable, we don't perform surgery in women with endometriosis
- ☐ Excision/ablation of peritoneal endometriosis
- ☐ Ovarian endometrioma
- ☐ Deep endometriosis of the bladder and/or bowel
- ☐ Endometriosis in umbilicus
- ☐ Endometriosis in caesarean section scar
- ☐ Other sites, please specify.....

Is a multidisciplinary treatment of endometriosis effectuated in your hospital? If so, which disciplines are involved consistently (i.e. in a dedicated team)? (You can select more than one answer)

- ☐ Dedicated collaboration with surgeon
- ☐ Dedicated collaboration with urologist

- ☐ Dedicated collaboration with gastroenterologist
- ☐ Dedicated collaboration with radiologist
- ☐ Dedicated collaboration with pain specialist
- ☐ Dedicated collaboration with psychologist
- ☐ Dedicated collaboration with dietician
- ☐ Dedicated collaboration with other health care professional, please specify
- ☐ No dedicated collaboration with other disciplines

Does your hospital collaborate with other hospitals with regard to endometriosis? If so, in which way is this collaboration effectuated? (you can select more than one answer)

- ☐ Yes, we collaborate regularly by email/phone with a certain hospital, i.e.
- ☐ Yes, we refer patients for surgical treatment to a certain hospital, i.e.
- ☐ Yes we refer patients for non-surgical treatment to a certain hospital, i.e.
- ☐ Yes, we refer patients for fertility treatment to a certain hospital, i.e.
- ☐ Yes, we operate our own patients in certain hospital, i.e.
- ☐ Yes, we are supported by professionals from other hospitals to operate our patients in our own hospital, i.e.
- ☐ No, we do not collaborate with other hospitals

How many patients are referred to another hospital for management of endometriosis each year?

.....

.....

Which patients are referred to another hospital? (you can select more than one answer)

- ☐ All patients with endometriosis
- ☐ Patients for whom treatment with analgesics is insufficient
- ☐ Patients for whom hormonal treatment is insufficient
- ☐ Patients with an indication for surgical treatment
- ☐ Patients in which surgical treatment was not sufficiently effective

- ☐ Patients with endometriosis and a desire for pregnancy
- ☐ Other patients, please specify
- ☐ We do not refer patients with endometriosis to another hospital

Miscellaneous

Is scientific research concerning endometriosis conducted in your hospital? If so, what is the topic of the research?

- ☐ Yes, please specify
- ☐ No

Are you in favour of the centralisation of endometriosis care in centres of expertise? Please specify your answer.

- ☐ Yes, because
- ☐ No, because

If you are in favour of centralisation of endometriosis care, how would you suggest effectuating this?

- ☐ Centres assigned by the Dutch Society of Obstetrics and Gynaecology (NVOG)/ profession
- ☐ Centres assigned by insurance companies
- ☐ Centres assigned by the government
- ☐ Other suggestion, please specify

If you are in favour of centralisation of endometriosis care, which criteria do you think should be applied for assignment? (you can select more than one answer)

- ☐ Number of new endometriosis patients per year, please specify
- ☐ Number of surgeries per year, please specify
- ☐ Multidisciplinary management of endometriosis
- ☐ Involvement in scientific research
- ☐ High patient satisfaction rates
- ☐ Recommendation by patient interest group

- o Other criteria, please specify

If you are in favour of centralisation of endometriosis care, what is your preferred approach?

- o A limited number of hospitals are designated as centre of expertise. Patients can be referred to these hospitals, for instance for further management/ surgical treatment
- o Different levels of expertise, for instance level 1 centre for basic diagnostics and treatment, level 2 centre for operative treatment of endometrioma and fertility treatment in women with endometriosis, level 3 centre for surgical management of complex/deep endometriosis
- o Regional collaboration in a network of expertise, in which basic management of endometriosis (both diagnostics and treatment) is conducted in some hospitals, and more advanced management in the centre of excellence of that particular region. Patients can move from one centre to another and back during the course of their treatment
- o Other approach, please specify

Guideline adherence

Are you familiar with the ESHRE guideline “Management of women with endometriosis”, which is adopted by the Dutch Society of Obstetrics and Gynaecology (NVOG)?

- o Yes
- o No

The ESHRE guideline presents a number of recommendations. A set of key recommendations was selected from the guideline by an expert panel of patients and professionals, as reported by Schleedoorn et al. Can you please report whether you are familiar with, agree with and adhere to these recommendations for each individual key recommendation? The recommendations are provided in the table at the next pages.

Key recommendation	Familiar with?	Agree with?	Adhere to?
Diagnostics			
Consider the diagnosis of endometriosis in the presence of gynaecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue in the presence of any of the above	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Consider the diagnosis of endometriosis in women of reproductive age with non-gynaecological cyclical symptoms (dyschezia, dysuria, hematuria rectal bleeding and shoulder pain)	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Assess ureter, bladder and bowel involvement by additional imaging if there is a suspicion based on history or physical examination of deep endometriosis, in preparation for further management	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Treatment of endometriosis associated pain			
Counsel women with symptoms presumed to be due to endometriosis thoroughly, and empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
<i>table continues</i>			

Prescribe hormonal treatment (hormonal contraceptives, progestagens, antiprogestagens or GnRH agonists) as one of the options, as it reduces endometriosis-associated pain	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Surgically treat endometriosis when identified at laparoscopy, i.e. 'see and treat', as this is effective for reducing endometriosis-associated pain	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
<i>table continues</i>			

Treatment of endometriosis associated subfertility			
Perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only in infertile women with AFS/ASRM stage I/II endometriosis, to increase ongoing pregnancy rates	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Perform excision of the endometrioma capsule, instead of drainage and electro coagulation of the endometrioma wall in infertile women with ovarian endometrioma undergoing surgery, to increase spontaneous pregnancy rates	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Use assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
<i>table continues</i>			

Miscellaneous			
Continue to treat women with a history of endometriosis after surgical menopause with combined estrogen/progestagen or tibolone, at least up to the age of natural menopause	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Fully inform and counsel women about any incidental finding of endometriosis	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never
Inform women with endometriosis, requesting information on their risk of developing cancer that (i) there is no evidence that endometriosis causes cancer, (ii) there is no increase in overall incidence of cancer in women with endometriosis and (iii) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Totally agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Totally disagree	<input type="radio"/> Always <input type="radio"/> Mostly <input type="radio"/> Often <input type="radio"/> Regularly <input type="radio"/> Sometimes <input type="radio"/> Never

Abstract

Study question

Which interventions appear to be most feasible for reducing diagnostic delay in endometriosis?

Summary answer

A set of key interventions to reduce the interval between onset of symptoms and the diagnosis of endometriosis was selected by an expert panel of professionals and patients

What is known already

Diagnostic delay in endometriosis is extensive. Several factors related to the delay have been identified, but a comprehensive strategy to convert these determinants into appropriate actions is lacking.

Study design, size, duration

Using a modified RAND Delphi method, this study reports on the systematic selection of a set of interventions directed at reducing diagnostic delay in endometriosis by an expert panel between August 2018 and March 2019.

Participants/materials, setting, methods

The expert panel consisted of patients (n=26) and professionals (n=55, of which 23 general practitioners, 26 gynaecologists and 6 miscellaneous professionals). They rated and prioritized 36 pre-identified interventions in four consensus rounds. Main outcome measure was a set of key interventions to reduce time between onset of symptoms and diagnosis.

Main results and the role of chance

A set of 10 interventions was selected from the initial set of 36 potential interventions. The selected interventions are directed at increasing awareness by educating medical professionals, increasing research efforts directed at non-invasive diagnostic tests, the development of a clinical guideline for general practitioners and gynaecologists and a decision aid directed at diagnostics. Response rates ranged between 79.0 and 96.2%.

Limitations, reasons for caution

Response bias may have occurred since not all panel members participated in all four rounds. Some interventions may have been difficult to appraise by specific subgroups of the panel.

Wider implications of the findings

The effectiveness of this set of interventions to reduce diagnostic delay in endometriosis, supported by a diversity of stakeholders in the field, can be evaluated in different health care settings internationally.

Study funding/competing interest(s)

None

Introduction

Epidemiologic studies indicate a prevalence of endometriosis in women of reproductive age of 2-10%^{1,2}. Endometriosis is a common cause of chronic pain and infertility.³ Unfortunately, the condition is characterized by a long interval between onset of symptoms and diagnosis.⁴⁻⁷ Determinants of this diagnostic delay are diverse and include factors related to the condition itself, like the variable symptom pattern and age of onset, whether or not subfertility is present and the fact that invasive diagnostic testing is the gold standard for diagnosis. Other factors contributing to the diagnostic delay are directed at patients' help seeking behaviour, medical professionals' knowledge and clinical strategies and the funding and organization of the health care system.^{4,6-9} The achievement of an earlier diagnosis is one of the research goals outlined by several groups of experts in the field of endometriosis.¹⁰⁻¹² Although the importance of developing an accurate non-invasive diagnostic test for endometriosis is obvious, in the meanwhile, attention should be paid to personal and clinical aspects of reaching a timely diagnosis as well. Results of previous studies have provided possible explanations for the lengthy delays in the diagnostic process. Literature about potential strategies to reduce the delay, however, is scarce and directed merely at one specific intervention or target audience.^{13,14} The selection of potential interventions is a delicate procedure, in which several factors need to be taken into account. First, it is impossible to develop a strategy based on evidence, since no direct evidence is available for the efficiency or feasibility of any intervention to reduce diagnostic delay in endometriosis. Furthermore, the diagnostic delay is multifactorial with a diversity of determinants at many different levels which results in preference for a multifaceted strategy.

In similarity to the development of quality indicators, the selection of interventions to reduce diagnostic delay in endometriosis is likely to benefit from a strategy which involves the opinion of different stakeholders, including both patients and health care professionals. Patients and professionals possibly have different views with regard to the best quality of care or a specific (clinical) strategy^{15,16} and combining these views may result in a wider range of knowledge and experience. Previous studies from our research group have identified factors related to the diagnostic delay in endometriosis,^{7,9,17-19} however, a comprehensive strategy to convert these determinants into appropriate actions is lacking. The aim of this study was to select key interventions as a first step in developing a strategy to

reduce diagnostic delay in endometriosis. As a secondary outcome measure, we aimed to detect differences in preferences with regard to possible interventions between patients and professionals.

Materials and Methods

Setting

A modified RAND Delphi procedure^{20,21} was used to select interventions most suitable for reducing diagnostic delay in endometriosis. The Delphi approach is a structured process to accumulate expert opinion with the use of a series of questionnaires to gather information. The questionnaires are submitted to an expert panel in rounds until group consensus is reached. Expert panels may be composed of stakeholders from different areas of expertise which can be included anonymously, thus avoiding domination of the consensus process by one or a few experts. The Delphi method is a validated instrument to reach consensus in situations where the evidence alone is insufficient. Although it is widely used to develop quality indicators in health care, the use of this method exclusively for the selection of key interventions is relatively new.²²⁻²⁸ In this study, the Delphi procedure was used to achieve consensus on the most preferable interventions for reducing diagnostic delay in endometriosis. Data capturing and management was conducted with Castor EDC.²⁹ Analysis were performed using IBM SPSS Statistics version 25.³⁰ The consensus procedure took place between August 2018 and March 2019.

Extraction of interventions

In the last years, our research group has performed several studies concerning diagnostic delay in endometriosis.^{7,17-19} Factors contributing to the delay, and corresponding interventions to reduce time to diagnosis were extracted from these studies and incorporated in a list of potential interventions to reduce the diagnostic delay in endometriosis. The list was supplemented with suggestions from experts during a brainstorm session, in which representatives from a national patient interest group and special interest group of the Dutch College of Gynaecologists participated. In addition, two general practitioners and a professor in patient-centred innovation were interviewed for input and a literature search for check on completeness was performed. The complete list consisted of 36 potential interventions, allocated to four domains: patient and professional awareness (n=17), patient behaviour (n=4), medical/scientific (n=10) and miscellaneous (n=5) (Appendix A).

Composition of the expert panel

We invited a diversity of health care professionals and patients for the expert panel by sending them an information letter and contact information for confirmation of their participation by email. Panel members were addressed individually and given the opportunity to participate anonymously. The professionals invited to the expert panel consisted of general practitioners, gynaecologists, and miscellaneous other specialists with special interest in endometriosis or patient-centeredness. Members of the multidisciplinary endometriosis teams from five of the hospitals with expertise in endometriosis were invited, including surgeons, urologists, anaesthesiologists and gastroenterologists. Patient representatives who are occupationally involved in endometriosis, for instance as board members of a patient interest group, were invited to participate as professionals. Endometriosis is diagnosed and treated in practically all hospitals, ranging from basic medical and operative treatment in general hospitals to more advanced treatment in clinics with special interest in endometriosis.¹⁷ Gynaecologists from all types of hospitals throughout the country, including general and tertiary care hospitals, participated as professionals in the expert panel. Patients were recruited from outpatient clinics from hospitals with expertise in endometriosis, the patient interest group and by advertisement on social media.

Delphi procedure

The list of potential interventions to reduce the delay was the basis of the first questionnaire round. The panel members received an email with a link to the online questionnaire for each round. At the beginning of the first round, the participants were asked to provide some background information regarding their personal, professional and relevant medical situation. Panel members who did not complete the first questionnaire were asked to provide this information in the second round. The Delphi procedure consisted of four rounds. The results of the analysis of the previous round served as input for the questionnaire that was used in the next round. Non-responders were sent a reminder after 7-10 days for the first three questionnaire rounds, and up to three reminders for the final round.

First questionnaire round

In the first round, all 36 potential interventions were presented to the expert panel in an online questionnaire. Panel members were asked to assess the individual interventions on relevance. Relevance was graded by the experts as to what extent the intervention was important and feasible in reducing

the interval between onset of symptoms and establishing the diagnosis of endometriosis on a 9-point Likert scale ranging from 1 (extremely irrelevant) to 9 (extremely relevant). An example of the score sheet is provided in Figure 1. In order to support discrimination between interventions with a high Likert score, the panel members were subsequently asked to compose a personal top-5 ranking of the interventions they considered the most relevant. Participants were given the opportunity to comment on their appraisal of the interventions and to add suggestions for additional interventions.

To what extent is the following intervention relevant in reducing the time between onset of symptoms and establishing the diagnosis of endometriosis?

You can move the slider by dragging it in the desired position. The associated score will become visible during the movement of the slider. The higher the score, the more relevant the intervention.

1. Increase awareness by education about menstruation/endometriosis at elementary school

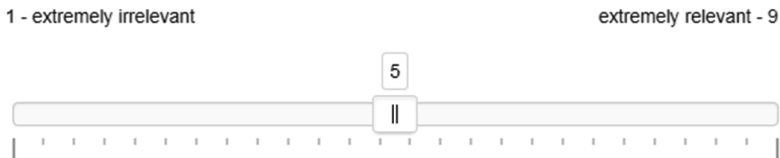


Figure 1. Example of score sheet

Example of intervention presented to the expert panel in the online questionnaire

Data analysis of the first round

The results of the first round were analysed using predefined criteria based on the literature.^{22,24,31} Each intervention was scored on three criteria: 1) a median rating of 8 or higher on the Likert scale, 2) panel agreement, and 3) a high ranking score. Panel agreement was based on the distribution of scores for each intervention and was confirmed if $\geq 75\%$ of panel members' individual scores were in the highest tertile of the Likert scale (7-8-9). Interventions should have at least 15% of the maximum ranking score to fulfil the third criterion. Ranking points were appointed to each top-5 ranking position; a number 1 position was appointed 5 points, number 2 position was appointed 4 points and so on until a number 5 position which was appointed 1 point. The sum of the received ranking points was converted into a percentage of the maximum ranking score. The maximum ranking score is defined as the

number of responding panel members multiplied by the points appointed to a number 1 position (5). For each intervention, these three scoring criteria were calculated, combined and converted into three possible outcomes: 'selected', 'rejected' and 'no consensus'. Intervention that fulfilled all three criteria were labelled as 'selected', interventions that met none were labelled as 'rejected' and interventions that met only one or two criteria were labelled 'no consensus'. Potential differences between the patients and professionals, or between the subgroups of participants in the expert panel (patients, general practitioners, gynaecologists and other professionals) were analysed using separate calculations of the three criteria for each categories. In addition, the Mann-Whitney U test was used for comparison of scoring behaviour in patients and professionals and the Kruskal-Wallis 1-way ANOVA for comparison between the three subgroups of professionals. If an intervention met all three criteria in at least one of the four subgroups, the intervention was labelled as 'selected by subgroup' even if the analysis of the complete expert panel came to a different conclusion. This created the opportunity for interventions with a strong subgroup preference to be reappraised by the rest of the panel. Additional interventions suggested by panel members were discussed by two of the researchers (MZ and AN) and, when considered of possible added value and feasible, incorporated in the second questionnaire for appraisal by the complete panel.

Second questionnaire round

The second questionnaire started with an overview of the items that were rejected and selected by the complete panel or a subgroup of experts in round one. The individual panel members were asked whether they agreed or disagreed with the decision of the panel for each intervention. The remaining interventions, which were labelled as 'no consensus' in the first round, and the additional interventions suggested by the panel members were resubmitted to the expert panel. The distribution of the scores of the panel members in round one were visualised in box-and-whisker plots, showing the spread in appreciation in patients and professionals combined with his or her own score in round one. Panel members who did not participate in the first round were provided with the box-and-whisker plots for patients and professionals. An example of a personalised box-and-whisker plot is given in Figure 2. All panel members, including the non-responders of round one, were asked to rate the 'no consensus' interventions again on a 9-point Likert scale, and were encouraged to revise their opinion considering the provided information.. The last part of the second questionnaire consisted of the personal top-3

ranking of interventions submitted in the current round (the 'no consensus' and newly added interventions). Panel members were given the opportunity to clarify their response at the end of the questionnaire.

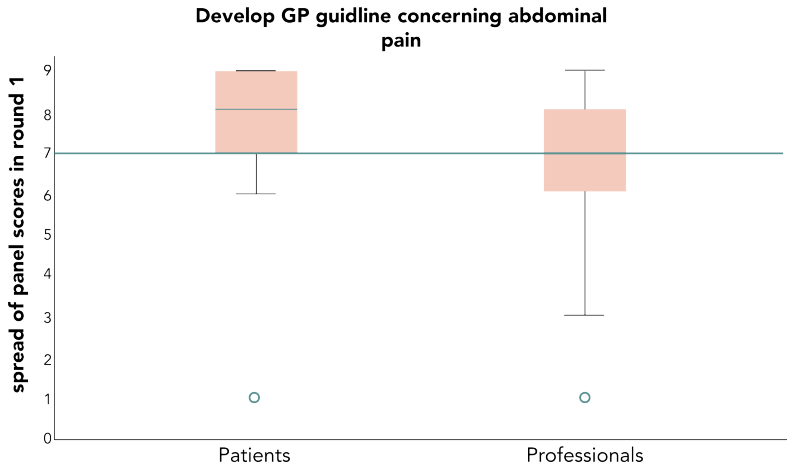


Figure 2. Example of personalised box-and-whisker plot

The box displays the range in which 50% of panel members scored the intervention, including the median score which is visible as the black line within the box. The 'T' or whiskers represent the opinion of 95% of the corresponding group of panel members (patients or professionals) and any outliers were visualised as dots. The panel member's own rating of the intervention in round one is represented by the horizontal green line.

Data analysis of the second round

The results of the second round were analysed using the same predefined criteria as used in round one: median rating of 8 or higher, panel agreement ($\geq 75\%$ of panel members in upper tertile) and ranking score percentage $\geq 15\%$. For each intervention, all three scoring criteria were calculated, combined and converted into two possible outcomes: interventions that fulfilled all three criteria in either the complete expert panel or at least one of the subgroups were labelled as 'selected', interventions that met less than three criteria were labelled 'rejected'. Furthermore, if $\geq 15\%$ of panel members disagreed with the selection or rejection of a specific intervention in round one, this intervention was relabelled as 'no consensus'. As in the first round, the Mann–Whitney U and Kruskal–Wallis 1-way ANOVA

tests were used to explore differences in scoring behaviour between patients and professionals.

Third questionnaire round

The third questionnaire round started with an overview of the interventions selected in the first and second round. Participants were asked whether they agreed with this preliminary set of interventions selected by the expert panel. Furthermore, the panel members were given the opportunity to either select one additional intervention from the list of 'no consensus' items remaining after analysis of the second round or to agree with the current set of interventions.

Data analysis of the third round

An intervention was added to the existing set of interventions if $\geq 15\%$ of the complete panel selected the item in the third round. The final set of interventions thus consisted of the selected interventions from the three subsequent rounds.

Fourth questionnaire round

Finally, all panel members who participated in at least one of the prior questionnaire rounds received an overview of the selected interventions by email. They were asked for their approval of the final set of interventions. The set consisted of interventions selected in the previous rounds. Four selected items related to indications for referral and guideline development were combined into one new intervention "Development of a guideline concerning menstrual complaints" in order to maintain the applicability of the intervention. Experts who disagreed were contacted to elaborate on their opinion.

Results

We invited 222 experts to participate in the expert panel, of which 81 agreed. The expert panel consisted of 26 patients and 55 professionals. The group of professionals was composed of 23 general practitioners (GPs), 26 gynaecologists and six miscellaneous or "other" professionals. The category "other professionals" was composed of two board members of the national patient interest group (one of them a patient herself), one behavioural scientist and lifestyle coach specialized in endometriosis (also a patient), a professor in patient-centred innovation, and two medical specialists who participate

in the multidisciplinary endometriosis team of a hospital with expertise in endometriosis: a urologist and a gastro-enterologist. The response rate to the invitation letter and composition of the expert panel is given in figure 3. In order to maintain the balance in the composition of the panel, we stopped including patients after 26 consecutive consents. Women who sent their informed consent after this stop were not allowed to participate (n=3). Two of the gynaecologists who initially consented to participate withdrew: one because of a lack of time, the other did not reply to any of the emails without justification.

Baseline characteristics of participants are shown in table 1 for patients and table 2 for professionals. Of the participating patients, 68% were diagnosed with endometriosis within the past five years and 52% had a diagnostic delay of more than ten years. Eighteen women (76.9%) had received treatment for endometriosis-associated pain, and eleven (44%) were treated for subfertility. Of the GPs, sixteen (69.6 %) did not have a subspecialisation, five (21.8%) completed a two-year postgraduate training on urogynaecology and two (8.7%) had another subspecialisation. The gynaecologists were working in the fields of reproductive endocrinology (n=2, 8.3%), benign gynaecology (n=13, 52.2%) or both (n=8, 33.3%), and one was a senior resident. Most gynaecologists (n=20, 83.3%) were members of the special interest group on endometriosis of the Dutch Society of Obstetrics and Gynaecology.

All experts who agreed to participate were invited to complete the questionnaire of all four rounds, irrespective of their participation in the previous rounds. The response rates for the online questionnaires are given in Figure 3. A summary of the results of the four questionnaire rounds is given in Figure 4 and Table 3.

Delphi round one

In the first Delphi round, 73 of the 81 (90.1%) members of the expert panel completed the online questionnaire. The response rates were 96.2% for patients and 87.3% for professionals. Data analysis resulted in the selection of six interventions and the rejection of 20 interventions (Table 3). Of the six selected interventions, five were selected from the domain "patient and professional awareness" and one from the domain "medical/scientific". The remaining 10 interventions were labelled 'no consensus' (Table 3). The Mann-Whitney U-test showed significant differences in rating between patients and professionals for 24 interventions. All of these interventions were rated higher

by patients as compared to the professionals. Differences in rating between the subgroups of professionals as analyzed by the Kruskal-Wallis were seen for 12 interventions. Detailed results of the subgroup analysis are provided in Appendix B. Two interventions were selected based on the results of the subgroup analysis: "Increase awareness by education about menstruation/ endometriosis at secondary school" fulfilled all three selection criteria in patients and the subgroup other professionals, the intervention "Develop joint guideline for GPs and gynaecologists concerning endometriosis" fulfilled all three criteria in the subgroup general practitioners. Five additional interventions were suggested by panel members, of which two were submitted to the expert panel in the second round and three were not adopted.

Table 1. Baseline characteristics patients

Patients (n=25)	
Age (y)	36.4 (6.8)
Educational level*	
Low	1
Average	16
High	8
Time since diagnosis (y)	4.4 (3.7)
Diagnostic delay (y)	12 (7.8)
Reason for referral to a gynaecologist	Number of women
Subfertility	6
Pain	10
Subfertility and pain	4
Other	4
Not applicable	1

Data are given in mean (standard deviation) unless stated otherwise.

* Information concerning educational level is given as absolute number of participants for each category

Delphi round two

In the second Delphi round, 64 out of 81 (79.0%) members of the expert panel started the online questionnaire. The response rates were 92.3% for patients and 72.7% for professionals (Figure 3). Eight participants (four patients and four professionals) started the questionnaire, but did not finish it completely. Data analysis resulted in the selection of seven interventions and the rejection of five interventions (Table 3). Three of the selected interventions were from the domain "patient and professional awareness" and four were from the

Table 2. Baseline characteristics professionals

	General Practitioners (n=23)	Gynaecologists (n=24)	Other professionals (n=6)
Age (y)	44.0 (9.9)	46.5 (8.8)	45.5 (6.5)
Gender (n)			
Male	5	8	3
Female	18	16	3
Subspecialisation (n)			
None	16		
(uro)Gynaecology	5		
Reproductive medicine		2	
Benign gynaecology		13	
Benign and Reproductive		8	
Other	2	1	3
Not applicable	0	0	3
Type of institution (n)			
Academic hospital		11	
Community teaching hospital		9	
Community hospital		3	
Other		1	
Years of experience	11.2 (8.5)	11.3 (7.9)	12.8 (7.2)
New endometriosis patients# (n)			
0-5	20	0	3
5-10	3	2	1
10-20	0	0	0
20-50	0	8	0
50-100	0	9	0
100+	0	5	0
Not applicable			2

Data are given as mean (standard deviation) unless stated otherwise

Number of patients with a new diagnosis of endometriosis per year

domain "medical/scientific". Two interventions were selected based on fulfilment of all three selection criteria by a subgroup of the expert panel: "Increase post academic education for other medical specialists" was selected by gynaecologists, "Develop GP guideline concerning abdominal pain" was selected by the general practitioners. The Mann-Whitney U test showed significant differences in rating between patients and professionals

for four interventions. These interventions were rated higher by patients as compared to the professionals. The Kruskal-Wallis analysis showed a significant difference in rating between the subgroups of professionals for one intervention. Detailed results of the subgroup analysis are provided in Appendix C. Six interventions were labelled ‘no consensus’ based on the disagreement of the expert panel with the selection or rejection of these interventions in round one.

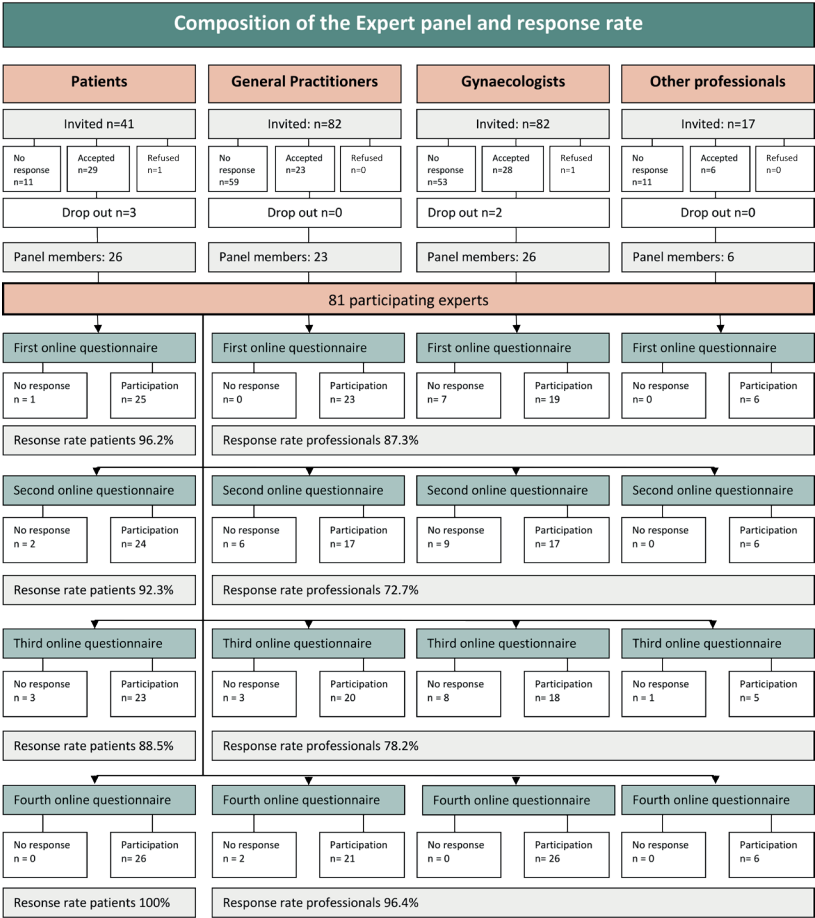


Figure 3. Composition of expert panel and response rate for each Delphi round

Selection of interventions to reduce diagnostic delay in endometriosis

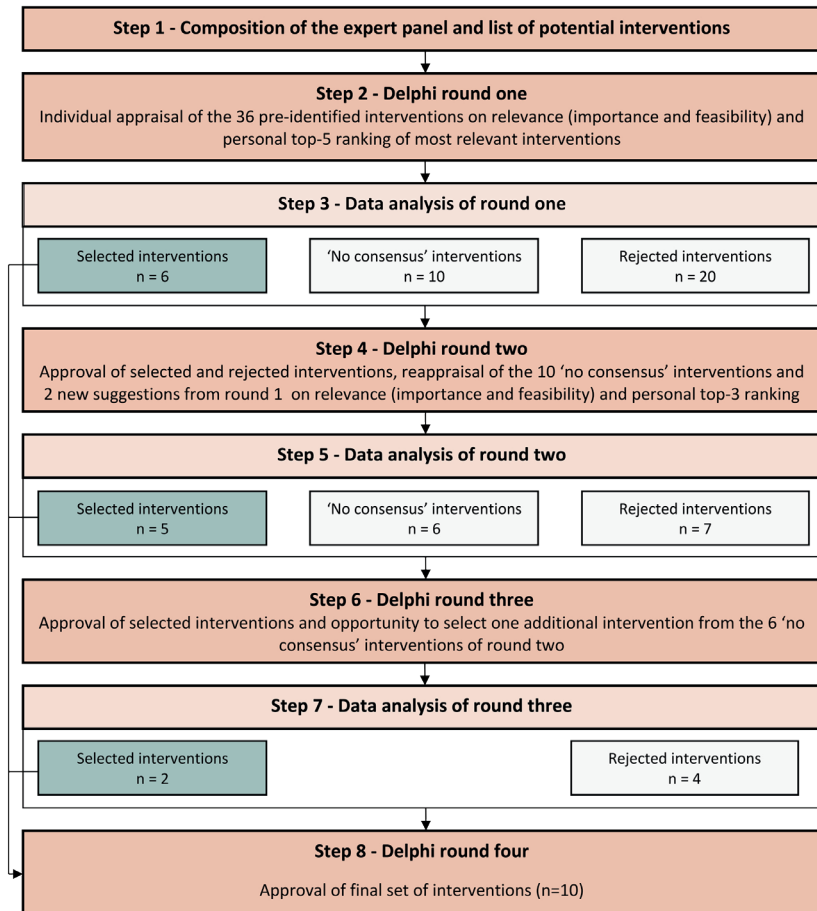


Figure 4. Delphi procedure for the selection of interventions

Table 3.Results of the analysis of each questionnaire round

Intervention	Round 1	Round 2	Round 3
Domain "patient and professional awareness"			
Increase awareness by education at elementary school	Rejected	Confirmed	
Increase awareness by education at secondary school	Selected [#]	No consensus	Rejected
Increase awareness by education at public health service/ school medical officer	Rejected	Confirmed	
Increase awareness by publicity at social media	No consensus	Rejected	
Increase awareness by publicity in magazines	Rejected	Confirmed	
Increase awareness by publicity on television	Rejected	No consensus	Rejected
Increase awareness using a celebrity for media attention	Rejected	Confirmed	
Provide education with commercial products (for instance in sanitary products)	Rejected	Confirmed	
Increase knowledge about the existence of the patient interest group	Rejected	No consensus	Rejected
Increase education in the general curriculum for medical students	Selected	Confirmed	
Increase education in the curriculum for general practitioner (GP) trainees	Selected	Confirmed	
Increase education about endometriosis in the curriculum for gynaecology residents	Selected	Confirmed	
Increase post academic education for general practitioners by specialized GPs	No consensus	Selected	
Increase post academic education for GPs by gynaecologists	Selected	Confirmed	

table continues

Increase post academic education for gynaecologists	No consensus	Selected	
Increase post academic education for other medical specialists	No consensus	Selected*	Selected
Increase number of scientific publications in medical journals and at conferences	Rejected	No consensus	Rejected
Domain "patient behaviour"			
Promote timely consultation with GP by media campaign	Rejected	Confirmed	
Promote timely consultation with GP by expanding website with layman information	Rejected	Confirmed	
Promote adequate preparation for consultation with GP (questionnaire/ diary)	Rejected	Confirmed	
Promote adequate preparation for consultation with gynaecologist	No consensus	Rejected	
Domain "medical/scientific"			
More research directed at non-invasive diagnostic tests	No consensus	Selected	
Advise GPs when to refer patients to a gynaecologist	No consensus	Selected	
Increase detection rate using information in digital patient records at GP offices	Rejected	Confirmed	
Communication platform for dialogue between GPs and gynaecologists	Rejected	Confirmed	
Teach gynaecologists in performing diagnostic tests	No consensus	Rejected	
Improve quality of correspondence letters from gynaecologists to GPs	Rejected	Confirmed	
Develop GP guideline concerning menstrual complaints	No consensus	Selected	
Develop GP guideline concerning abdominal pain	No consensus	Selected^s	
<i>table continues</i>			

Develop joint guideline for GPs and gynaecologists concerning endometriosis	Selected*	Confirmed	
Develop decision aid/diagnostics aid for patients and GPs to use during consultation	Rejected	No consensus	Selected
Domain "miscellaneous"			
Introduce layman's term for endometriosis	Rejected	Confirmed	
Develop website with information for women with abdominal complaints	Rejected	Confirmed	
Develop website with detailed information and literature for medical professionals	Rejected	Confirmed	
Develop online community with option to interact with professional	Rejected	Confirmed	
Develop mobile device application to record symptoms	Rejected	No consensus	Rejected
Introduce gynaecology internship for general practice trainees		Rejected	
Put endometriosis on the agenda at government/politics		Rejected	

Selected by subgroups patients and other professionals

* Selected by subgroup gynaecologists

\$ Selected by subgroup general practitioners

Delphi round three

In the third Delphi round, 66 out of 81 (81.5%) members of the expert panel completed the online questionnaire. The response rates were 88.5% for patients and 78.2% for professionals. A majority of the panel members (63/66, 95.5%) agreed with the preliminary selection of interventions from the first two rounds. The three panel members who did not agree with the preliminary set of interventions were all professionals (one GP, one gynaecologist and one other professional). They provided an explanation for their disagreement but this did not lead to a change in the composition of the set because of the limited number of disagreeing experts. Forty-four panel members selected an additional intervention to the preliminary set. Data analysis resulted in the selection of two of these interventions into the final set of recommendations: "Increase post academic education for other medical specialists" and

“Develop decision aid/diagnostics aid for patients and GPs to use during consultation”. The interventions were from the domains “patient and professional awareness” and “medical/scientific”.

Delphi round four

Thirteen interventions were selected from the first three rounds, of which four were combined into one intervention concerning guideline development. The final set therefore consisted of ten interventions, which were submitted to the complete expert panel (Box 1). The selected interventions were from the domains “patient and professional awareness” (n=7) and “medical/scientific” (n=3). No interventions were selected from the domains “patient behaviour” and “miscellaneous”. In the fourth Delphi round, 79 panel members evaluated the final set of interventions. Of the responding participants, 76 (96.2%) approved the final set of selected interventions. Two panel members did not agree and one panel member abstained from assessment. The panel members who did not agree were both gynaecologists. Reasons for disagreement were a lack of interventions directed at online distribution of information in order to increase awareness and an excessive focus on medical staff instead of the involvement of patients, the society and the patient interest group. The panel member who abstained from assessment was from the subgroup of “other professionals”. This panel member stated that he was not able to make a reasonable judgement based on his knowledge.

Discussion

To our knowledge, this is the first report on the selection of interventions aimed at reducing the diagnostic delay of endometriosis and can be seen as a first step in the development of a targeted strategy to reduce this delay. The study was directed exclusively at factors related to the timely diagnosis of endometriosis, other aspects of endometriosis care were not taken into account.

The multidimensional set of key interventions selected by the expert panel covers the education of health care professionals from the basic curriculum for medical students up to post academic training for clinical specialists, the development of an interdisciplinary clinical guideline, the design of a decision aid for guidance during consultations and expansion of scientific research directed at non-invasive diagnostic tests. Differences in scoring behaviour were seen between patients and professionals, and between

the different subtypes of professionals, which yielded rich and in-depth information regarding the value and feasibility of interventions. During the subsequent stages of the Delphi procedure, these differences appeared to diminish. One of the strengths of the study is the size and diversity of the expert panel, in which both patients and medical professionals with a variable background participated. In different contexts, the value of involving patients in the development of quality indicators has been established previously.^{32,33} The literature shows that diversity of expert panel members leads to better performance as this may allow the consideration of different perspectives.^{34,35} The differences seen in the rating of interventions between patients and professionals confirm the importance of involving this diversity of panel members. Although two of the “other professionals” are affected by endometriosis themselves, they were classified as professionals instead of patients because they are occupationally involved in endometriosis, and therefore considered capable of representing not merely their own personal opinion but to reflect on the matter from a wider perspective. They were instructed to complete the questionnaires from the professional perspective, although their personal experience might have influenced their appraisal to a certain degree.

The fact that that specialists tend to favour the interventions with which they are most familiar,³⁵ was apparent during the rating of potential interventions but did not obstruct panel agreement. Some of the interventions were rather specific and therefore difficult to evaluate by specific subgroups. For example, the content of the medical education or quality of correspondence letters are impossible to assess by patients. On these occasions, the subgroup analysis and structured feedback is of great importance for fine-tuning the intervention strategy. One of the interventions, which was supported in particular by the patients but did not make it to the final set of interventions was “increase awareness by education at secondary schools”. Given the strong patient preference related to this item, and the fact that other countries have implemented comparable initiatives with seemingly positive results, it will be of interest to keep this in mind.¹³ Another example of the value of the subgroup analysis is the fact that GPs appear to appreciate the quality of information given on the primary care layman’s website more than the other professionals. This may be explained by the fact that they will probably benefit more from the effect of such an intervention than the gynaecologists or other professionals. The particular website, which is a high quality evidence-based health information website launched by the Dutch College of General

Practitioners, has been shown to reduce health care usage and improve self-management.³⁶ It is possible that this website is not widely known amongst gynaecologists and other secondary care professionals, which could explain the difference in appraisal as well.

Box 1. Final set of selected interventions

Key interventions selected by the expert panel	Selected in round
Patient and professional awareness	
Increase education in the general curriculum for medical students	1
Increase education in the curriculum for general practitioner (GP) trainees	1
Increase education about endometriosis in the curriculum for gynaecology residents	1
Increase post academic education for general practitioners by specialized GPs	2
Increase post academic education for GPs by gynaecologists	1
Increase post academic education for gynaecologists	2
Increase post academic education for other medical specialists	3
Medical/scientific	
More research directed at non-invasive diagnostic tests	2
Develop guideline concerning menstrual complaints including indications for referral	1-2
Develop decision aid/diagnostics aid for patients and GPs to use during consultation	3

The observation that the patients seemed to focus more on awareness in medical professionals than the general population was surprising. It might result from the fact that these women reflect on their experience with medical professionals during the diagnostic process. Several studies have reported on multiple consultations, misdiagnosis and not feeling acknowledged preceding the eventual diagnosis of endometriosis.^{4,37,38} These issues were frequently disclosed by the participating patients in the comments section at the end of the first round questionnaire. However, the general population

obviously benefits from educating medical professionals as well. Information about normal menstruation and which symptoms may reflect a condition such as endometriosis can be provided by GPs, for example during consultations concerning contraception. In general, medical professionals play an important role in population-wide health education and patient empowerment. The efforts of patient interest groups are equally important, and collaboration between medical professionals and patient interest groups can lead to the transmission of high quality information about both physiological and pathological aspects of menstruation and reproduction on a wide variety of occasions.

Some limitations related to the design of the study need to be considered. First, it is likely that from the invited professionals, those who are most interested in endometriosis have responded. It is unclear whether this has influenced the results. However, efforts have been made to successfully include professionals from different types of hospitals and practices, and there is some evidence that agreement to participate in consensus development groups is unrelated to years since qualification, specialty, sex or level of degrees.³⁹ Second, although the response rates were high, some response bias may have occurred as not all panel members took part in all four rounds mainly because of time restriction and complexity of the procedure. Especially the second round questionnaire, in which panel members were provided with graphic individual and group feedback, appeared challenging for some of the panel members. A number of interventions required detailed knowledge of for instance the education program of medical professionals or the organization of health care, which may pose difficulties in the assessment of these interventions by patients. This might have led to a more prominent role of the most motivated panel members and higher educated patient representatives. Finally, the completeness of the list of interventions is a point of discussion. The extraction of potential interventions from the literature and experts' opinion was done with great care, but the list submitted to the expert panel may not be completely comprehensive. Future interventions should be adapted to fit the needs of specific circumstances in different regions with regard to organization of health care or cultural beliefs. For instance, interventions directed at the education of general practitioners may not apply to countries without a strongly positioned primary care. Overall, the results of the consensus procedure are likely to be applicable in other countries, given the diversity of the expert panel and similarities in health care organization in many developed countries, as well as the versatile target audience of the selected interventions.

In conclusion, the present study resulted in a set of key interventions to reduce diagnostic delay in endometriosis from the domains “patient and professional awareness” and “medical/scientific”. The set is supported by a diversity of stakeholders in the field of endometriosis. Further efforts should be made to incorporate these interventions in a multifaceted strategy aimed at optimizing help seeking behaviour of women with symptoms suggestive of endometriosis, and improving knowledge and clinical strategies in medical professionals.

Contribution to authorship

MZ, WN, DB and AN contributed to the design of this study. MZ, LK, JV and AN prepared the questionnaires. MZ, AN and WN analyzed the data, and all the other authors contributed to the interpretation of the data. MZ drafted the manuscript and WN, DB and AN made substantial contributions to it. All the authors critically revised the manuscript and approved the version to be published.

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Appendices

Appendix A. Complete list of potential interventions

Patient and professional awareness

Increase awareness by education about menstruation/endometriosis at elementary school

Increase awareness by education about menstruation/endometriosis at secondary school

Increase awareness by education at public health service/ school medical officer

Increase awareness by publicity at social media

Increase awareness by publicity in magazines

Increase awareness by publicity on television

Increase awareness using a celebrity for media attention

Provide education with commercial products (for instance in sanitary towels/ tampons)

Increase knowledge about the existence of the patient interest group

Increase education about endometriosis in the general curriculum for medical students

Increase education about endometriosis in the curriculum for general practitioner (GP) trainees

Increase education about endometriosis in the curriculum for gynaecology residents

Increase post academic education for general practitioners by specialized GPs

Increase post academic education for GPs by gynaecologists

Increase post academic education for gynaecologists

Increase post academic education for other medical specialists, for instance gastro-enterologists and urologists

Increase number of scientific publications concerning endometriosis in medical journals and at conferences

Patient behaviour

Promote timely consultation with GP by media campaign

Promote timely consultation with GP by expanding website with layman information advocated by GPs (www.thuisarts.nl)

Promote adequate preparation for consultation with GP (questionnaire/ diary)

Promote adequate preparation for consultation with gynaecologist (questionnaire/diary)

Medical/scientific

More research directed at non-invasive diagnostic tests

Advise GPs when to refer patients to a gynaecologist

Increase detection rate using information in digital patient records at GP offices

Communication platform for dialogue between GPs and gynaecologists

Teach gynaecologists in performing diagnostic tests

Improve quality of correspondence letters from gynaecologists to general practitioners

Develop GP guideline concerning menstrual complaints

Develop GP guideline concerning abdominal pain

Develop joint guideline for GPs and gynaecologists concerning endometriosis

Develop decision aid/diagnostics aid for patients and GPs to use during consultation

Miscellaneous

Introduce layman's term for endometriosis

Develop website with information for women with abdominal pain and/or menstrual complaints

Develop website with detailed information and literature for medical professionals

Develop online community with option to interact with professional

Develop mobile device application to record symptoms

Participants' suggestions from round one

Adopted and incorporated in second round questionnaire:

Put endometriosis on the agenda at government/politics

Introduce gynaecology internship for general practice trainees

Not adopted:

Keeping track of absence because of menstruation at schools and sports facilities

Collaborate with other patient interest groups (Women's Inc, Freya etc)

Set up Women's Health clinics for family planning, contraception, sexuality and menstrual complaints

Appendix B. Subgroup analysis round 1

Intervention	Median score patients	Median score professionals			Conclusion
		Overall			
		GP	GYN	OP	
Patient and professional awareness					
Increase awareness by education at elementary school	5	2			Rejected ^a
		2	3	2.5	
Increase awareness by education at secondary school	8	7			Selected ^{a,b}
		6	8	8	
Increase awareness by education at public health service/ school medical officer	7	6			Rejected ^b
		4	7	7	
Increase awareness by publicity at social media	8	7			No consensus ^{a,b}
		5	7	7.5	
Increase awareness by publicity in magazines	8	6			Rejected ^{a,b}
		5	7	7	
Increase awareness by publicity on television	8	5			Rejected ^{a,b}
		2	6	7.5	
Increase awareness using a celebrity for media attention	6	6			Rejected ^b
		3	7	7.5	
Provide education with commercial products (for instance in sanitary products)	7	4			Rejected ^{a,b}
		2	5	5	
Increase knowledge about the existence of the patient interest group	7	6			Rejected ^{a,b}
		5	7	8	
Increase education in the general curriculum for medical students	9	8			Selected ^a
		8	8	8	
Increase education in the curriculum for general practitioner (GP) trainees	9	8			Selected ^a
		8	8	8	
Increase education about endometriosis in the curriculum for gynaecology residents	9	8			Selected ^a
		8	8	8	

table continues

Increase post academic education for general practitioners by specialized GPs	9	8	8	7	No consensus ^a
Increase post academic education for GPs by gynaecologists	9	8	8	8	Selected
Increase post academic education for gynaecologists	9	7	7	7.5	No consensus ^a
Increase post academic education for other medical specialists	8	8	7	8	No consensus ^a
Increase number of scientific publications in medical journals and at conferences	8	6	6	7.5	Rejected ^a
Patient behaviour					
Promote timely consultation with GP by media campaign	8	6	5	7.5	Rejected ^{a,b}
Promote timely consultation with GP by expanding website with layman information	8	7	8	7.5	Rejected ^b
Promote adequate preparation for consultation with GP (questionnaire/ diary)	7	7	7	7.5	Rejected
Promote adequate preparation for consultation with gynaecologist	8	8	7	8	No consensus
Medical/scientific					
More research directed at non-invasive diagnostic tests	9	8	8	8	No consensus ^a
Advise GPs when to refer patients to a gynaecologist	9	8	8	8	No consensus ^a
Increase detection rate using information in digital patient records at GP offices	9	7	6	7.5	Rejected ^a
Communication platform for dialogue between GPs and gynaecologists	8	7	6	8	Rejected ^a
Teach gynaecologists in performing diagnostic tests	9	7	7	7.5	No consensus ^a
Improve quality of correspondence letters from gynaecologists to GPs	8	7	7	5	Rejected ^a

table continues

Develop GP guideline concerning menstrual complaints	8	8				No consensus
		8	8	8		
Develop GP guideline concerning abdominal pain	8	7				No consensus
		8	7	7		
Develop joint guideline for GPs and gynaecologists concerning endometriosis	8	8				Selected
		8	8	8		
Develop decision aid/diagnostics aid for patients and GPs to use during consultation	7	7				Rejected
		7	7	7.5		
Miscellaneous						
Introduce layman's term for endometriosis	8	3				Rejected ^a
		2	3	4		
Develop website with information for women with abdominal complaints	7	6				Rejected ^b
		5	6	7.5		
Develop website with detailed information and literature for medical professionals	8	6				Rejected ^a
		6	6	7.5		
Develop online community with option to interact with professional	8	5				Rejected ^{a,b}
		4	5	7.5		
Develop mobile device application to record symptoms	7	7				Rejected
		6	7	7.5		

^a represents a statistical difference in median rating between patients and professionals as analyzed by the Mann Whitney-U test (p-value < 0.05)

^b represents a statistical difference in median rating between subgroups of professionals as analyzed by the Kruskal-Wallis 1-way ANOVA (p-value < 0.05)

GP: general practitioners. GYN: gynaecologists. OP: Other professionals

Appendix C. Subgroup analysis round 2

Intervention	Median score patients	Median score professionals			Conclusion
		Overall			
		GP	GYN	OP	
Patient and professional awareness					
Increase awareness by publicity at social media	8	6			Rejected ^a
		4	6	7	
Increase post academic education for general practitioners by specialized GPs	8	8			Selected
		8	8	8	
Increase post academic education for gynaecologists	8	7			Selected ^a
		7	7	8	
Increase post academic education for other medical specialists	8	7			Selected
		7	8	7	
Patient behaviour					
Promote adequate preparation for consultation with gynaecologist	7	7			Rejected
		7	8	7	
Medical/scientific					
More research directed at non-invasive diagnostic tests	8	8			Selected
		8	8	8	
Advise GPs when to refer patients to a gynaecologist	8	8			Selected
		8	8	7	
Teach gynaecologists in performing diagnostic tests	8	7			Rejected ^a
		7	7	7	
Develop GP guideline concerning menstrual complaints	8	8			Selected
		8	8	8	
Develop GP guideline concerning abdominal pain	8	7			Selected
		8	7	7	
Introduce gynaecology internship for general practice trainees	7	7			Rejected
		7	7	7	

table continues

Miscellaneous					
Put endometriosis on the agenda at government/politics	8	<div>5</div> <div>468</div>			Rejected ^{a,b}

^a represents a statistical difference in median rating between patients and professionals as analyzed by the Mann Whitney-U test (p-value < 0.05)

^b represents a statistical difference in median rating between subgroups of professionals as analyzed by the Kruskal-Wallis 1-way ANOVA (p-value < 0.05)

GP: general practitioners. GYN: gynaecologists. OP: Other professionals

In this thesis the determinants of the diagnostic delay of endometriosis in the Netherlands were studied from the perspective of the patient (chapters two and three), the general practitioner (chapters four and five) and the gynaecologist (chapter six). Opportunities to decrease the delay were evaluated by an expert panel of both patients and professionals in chapter seven. The relevance and clinical implications of the findings obtained in these studies as well as the future perspectives are discussed in this chapter in a multidimensional approach.

If I were a woman

As a woman, I want to be well informed about my own body and health. I believe that general information about the anatomy and function of the female reproductive system should be provided to me from a young age onwards, because this will make it easier for me bring this up if necessary. This information can be given at home, by my parents or other caregivers especially during puberty and adolescence. In addition, this topic should be addressed at my school as well. Age appropriate information about the physiology of normal menstruation, including possible associated symptoms, should be provided to me either by teachers or health care providers. It is important for me to learn which discomforts are within the normal range, and when to seek medical help.

Information regarding possible gynaecologic conditions, especially those with a high prevalence rate or large impact on wellbeing should be provided to both boys and girls. Since endometriosis is one of the most prevalent benign gynaecologic conditions, with symptoms often starting at young age, the importance of communicating with adolescents about this condition is obvious.^{1,2} The studies presented in this thesis stress the value of knowledge about normal menstruation and endometriosis in the general population, since the diagnostic delay of endometriosis is in part attributable to delayed disclosure of symptoms.³⁻⁵ A study from Shadbolt and co-workers indicated that a majority of young women advocate the education of teenagers about endometriosis, and they prefer obtaining this information from schools, the internet and magazines.⁶ There is some evidence that the introduction of a menstrual health education program increases awareness and promotes early helpseeking behaviour of young women.⁷ However, teenagers and adolescents may not feel comfortable to discuss these topics at school, and adequate information is not easily available on the internet.^{6,8} For this reason, it is of great

importance to make sure that the information that is given is age appropriate and aligned to the interest and cognition of the addressed age group.

If I were a pubertal or adolescent girl, I would like to be able to discuss my menstruation issues with my mother or other close relatives and friends. I would ideally compare the duration, severity and symptoms of my menstruation with those of peers, and be guided and supported in my decision to seek medical help. When I would visit my general practitioner, I would prefer a doctor who acknowledged the fact that I weighed my symptoms meticulously before planning a consultation, and be heard about the impact on my personal life. As an adult woman, I want my general practitioner to understand that although I am not keen on getting a gynaecologic examination, I do want to know whether something is wrong with me. And even though I may not get a definite diagnosis, I would like to be informed about the suspicion of having endometriosis before starting an empirical therapy and the effect this may have on my future fertility. I need to know when to return to the doctor in case the treatment doesn't have the desired effect or if I want to get pregnant, and discuss the pros and cons of having the diagnosis confirmed or ruled out by a specialist. On the other hand, I don't want to be frightened about possibly having a chronic condition which may or may not interfere with my quality of life or family planning. Having heard about endometriosis at school or at home will probably help putting this into perspective.

If I were a general practitioner

As a general practitioner, I want to be able to distinguish physiology from pathology. I see many patients each day, most of whom have minor or self-limiting health issues. Dysmenorrhea is the most prevalent gynaecologic symptom in women of reproductive age, but is not unequivocally related to a pathologic condition like endometriosis.^{9,10} Chronic pelvic pain syndromes are as prevalent in primary care as asthma or back pain.¹¹ Women with pelvic pain may have severe symptoms which negatively affect their quality of life, but the differential diagnosis is wide, and a proportion of these women may not have an underlying condition after all. Frequently, associated symptoms like fatigue, abdominal bloating or periodic constipation are presented as well, which may point to other conditions like irritable bowel syndrome, or even somatisation.¹² Like most general practitioners, I had some education about endometriosis at medical school, but it appears to me as if I don't see many women with this condition at my clinic.

Endometriosis is problematic in the primary care setting for various reasons. Patients initially present to their general practitioner not with endometriosis, but with a combination of symptoms that could be the result of a variety of conditions. The extent of disease does not necessarily correlate with the severity of symptoms, and women may be diagnosed opportunistically when presenting with other problems, for example infertility. They may have extensive disease, but only mild or even absent symptoms and vice versa. This scenario does not correspond to common expectations of disease and presenting symptoms. Since for many women the occurrence of their symptoms coincides with menstruation, general practitioners may have a tendency to trivialize symptoms and consider them as 'normal' discomforts. This normalisation can result in symptom control rather than a search for a diagnosis. On average, women with endometriosis report seven visits to their general practitioner before being referred to a specialist, and nearly three-quarters of women experience misdiagnosis.^{13, 14} It is for these reasons, amongst others, that unsatisfactory experiences within the primary care setting are common.^{5, 15, 16} Qualitative studies in women with endometriosis revealed that many of them felt that their symptoms were not taken seriously despite frequent encounters with a general practitioner, and perceived a long-term struggle to receive an appropriate referral.

As a general practitioner, I would notice that some women do not return to my office, but I may not be aware of the underlying reason why some patients give up going to their doctor and choose to endure the pain until something triggers them to return.^{3, 5} One of my key objectives is to acknowledge all of my patients in their concerns and take them seriously. As I am the gate keeper for medical specialist care, it is important for me to consider which patients will require a referral for medical specialist care, and which can be managed in primary care. A close collaboration with gynaecologists will provide me with an easily accessible opportunity to discuss individual patients with a specialist to optimize the appropriate level of care. An adequate evaluation of a woman presenting with pelvic or menstrual complaints consists of a recording of the full spectrum of symptoms combined with a carefully conducted but complete gynaecologic evaluation, which is challenging given the limited consultation time. It appears that a majority of general practitioners does not feel confident in identifying signs consistent with endometriosis in speculum and bimanual examination, and many of them omit a gynaecological examination even if they suspect endometriosis.^{5, 17} The development of a widely available and accurate non-invasive diagnostic test for endometriosis may seem like the

holy grail for a timely diagnosis of endometriosis, but has some pitfalls as well. As a general practitioner, it is one of my responsibilities to prevent excessive interference with naturally occurring phenomena, unnecessarily turning women into patients. Overdiagnosis, overtreatment and the transformation of everyday complaints into abnormalities can lead to medicalisation. It can create anxiety, stigmatization, increased costs and side effects as a result of unnecessary treatment.^{18, 19}

However, every woman presenting with pelvic pain or symptoms related to the menstrual cycle merits an adequate appraisal and acknowledgement of her concerns. Consideration on the likelihood of an underlying pathological condition like endometriosis should be done with great care in order to prevent disease progression and subfertility. The development of a national multidisciplinary clinical guideline directed at pelvic pain and problematic menstruation, appropriate for general practitioners, will support the timely consideration of endometriosis and promote early referral to a gynaecologist for those who are at increased risk of endometriosis or subfertility. In women with mild symptoms without a desire for pregnancy, one should consider to start empirical therapy before the routine use of extensive diagnostic procedures. Subfertility and symptoms or signs indicating advanced disease require immediate referral. The choice between empirical treatment and advanced diagnostics or referral should ideally be made together with the patient. Incorporating patient preferences successfully into clinical strategies relies on improved knowledge of both women and medical professionals, and may be supported by the use of a decision aid, as advocated by an expert panel as described in this thesis.^{20, 21} Nevertheless, providing the general population and medical professionals with enough information to raise awareness without unnecessary medicalisation will remain a huge challenge.

If I were a gynaecologist

As a gynaecologist, I want to inform my patients on the chance of having endometriosis, explain the pros and cons of each step in the diagnostic process and offer them the most suitable treatment for their specific symptoms or subfertility. Personalized medicine and shared decision making are key elements of my daily clinical care.²¹ To be able to provide good quality diagnostics and treatment at a secondary care level, I was trained at medical school and during my specialty training in obstetrics and gynaecology. As a gynaecologist, I stay up to date by attending conferences and post-

academic education courses concerning endometriosis. A high quality national clinical guideline, including an overview of the most recent literature and recommendations for diagnosis and treatment, will support my clinical strategies in daily practice. Special attention should be paid to perform adequate and complete diagnostic tests. The basic gynaecologic examination should be done with great care since it may point to anatomic areas which need to be evaluated in more detail by ultrasound or other imaging techniques. In my opinion, the trans vaginal ultrasound should ideally be performed by the gynaecologist herself, since this facilitates the correlation of particular symptoms or site specific tenderness to endometriotic lesions. Based on the results of the history and clinical examination, the extent of endometriosis can be assessed with reasonable accuracy.^{22, 23} At this point, it is important to decide whether medical or fertility treatment is started or expanded, or more elaborate imaging (MRI) or diagnostic laparoscopy is indicated. This decision can be supported by discussing the complexity of the individual case within a regional network, in which both secondary and tertiary care clinics specialized in treating advanced endometriosis in a multidisciplinary team participate. Collaboration between clinics with varying degrees of expertise will promote the timely diagnosis and complete staging of endometriosis and allows for the appropriate treatment with as minimal number of surgeries as possible.^{24, 25} Especially in young women, it is wise to be cautious with (repeated) surgical interventions for endometrioma as this may have detrimental effects on their ovarian reserve. As a gynaecologist, I expect a rise in the number of referrals from general practitioners and other medical specialists, resulting from recent and future efforts to increase awareness on endometriosis.^{20, 26} These women should receive appropriate care at the appropriate institution. Women responding well to basic medical treatment can be further managed by their own general practitioner, which should receive a detailed overview of performed diagnostics and therapy, completed with specific advice on further actions in case of symptom recurrence or desire for pregnancy. Women with more advanced disease prompting specialist care should be treated in a center of expertise.

If I were a patient representative

Patient interest groups have traditionally provided a supporting role for patients, but their activities are constantly developing and evolving. Their core task is to supply comprehensive information for instance on paper, websites and social media and arrange for contacts with other patients to

share experiences and comfort. Besides the supporting and advising of individual patients, they become increasingly involved in the public, scientific and political domain as well. As a board member of the patient interest group for endometriosis, I would put a large amount of effort in increasing awareness. I would reach out to women, who have not been diagnosed with endometriosis, to make sure they are well informed about normal menstruation and when to seek medical help. Off course, this cannot be done alone and collaboration is very important. I would join efforts with a variety of health care providers, including public health services, general practitioners, paediatricians, and gynaecologists, to create an education program with age specific and comprehensive information to be enrolled at schools, sports clubs and social services. Relevant information can be concentrated on a dynamic online platform, which additionally provides an opportunity to interact with experts in the field. In my patient advocacy role, I would like to be involved in official bodies advising on health policy and scientific research strategies. The patient interest group could participate in raising funds for research or recruiting patients for clinical trials, and joint efforts of similar groups across countries can help set up international initiatives in this area.

If I were a policy maker

As a policy maker, I want to focus on a balance between good quality health care and the economic burden to society. Endometriosis is a chronic illness with an associated economic burden comparable to diabetes or Crohn's disease.²⁷ A large proportion of the costs result from absenteeism of work and loss of productivity. One could speculate that the real costs might even be higher, since approximately one third of menstruating women in the general population is not able to perform all their usual activities during their period and this probably includes women with endometriosis which have not yet been diagnosed or received a false diagnosis.¹⁰ The medical costs of endometriosis rise with increasing disease severity or infertility, suggesting that the appropriate management started after a timely diagnosis may reduce these costs.²⁷ Pragmatic treatment of women with menstrual symptoms affecting daily life with low cost, safe and effective medical treatment may reduce the need for advanced and expensive treatments and improve quality of life. I would encourage partnership between the patient interest group, medical community, media and other stakeholders to initiate strategies to promote awareness, support initiatives like the development of a new clinical guideline and decision aid, and maintain endometriosis on the research agenda.

If I were a post-doc researcher

As a post-doc researcher, I would realize that there is still a lot of work to be done. Efforts should be made to further elucidate the etiology of endometriosis, since this may lead to increased understanding of the evolution of the disease and create possible opportunities for new therapies. Research priorities should obviously include the development of diagnostic and treatment options.

In this thesis, factors contributing to the diagnostic delay of endometriosis and possible targets for reducing the interval between onset of symptoms and diagnosis are presented. The concept “diagnostic delay” remains difficult to quantify. Studies often rely on participants’ memory of the moment when symptoms emerged, which may be difficult to recall with exact accuracy. The patient delay can additionally be assessed by including documentation of symptoms in medical records or prospective recording of symptoms; however both may introduce a certain amount of bias. The identification of the exact moment of diagnosis is equally challenging. Obviously, establishing the diagnosis using the “gold standard” test of histological confirmation of tissue collected at laparoscopy represents an accurate timing of the definite diagnosis. However, suspicion on endometriosis may have arisen based on the presented symptoms or findings of the clinical examination or imaging. If this suspicion leads to the initiation of suppressive medical treatment, should this be considered a provisional diagnosis and therefore the end of the diagnostic period? Adapting this strategy in scientific studies can lead to contamination of the study population with women who may not actually have endometriosis. On the other hand, including women exclusively with laparoscopy proven endometriosis can lead to the selection of only the most severe cases, in which potentially women with a long period of unsuccessful pragmatic therapies are overrepresented. The discovery of a non-invasive diagnostic test with high sensitivity and specificity may overcome this issue. Unfortunately, although some progress is made in this area, no such test is on the verge of being introduced in clinical practice.²⁸ Given the evidence that genetic factors contribute to the individual susceptibility for endometriosis, and the progress that is currently being made in genome-wide association studies, genetic testing may become a cornerstone in identifying women with a predisposition to endometriosis.²⁹⁻³¹ A large amount of biomarkers in plasma, tissue or urine have been studied up to date, but none have shown to be of sufficient diagnostic potential yet. The same holds true for miRNAs.^{28, 32}

Ultimately, a combination of tests may allow for both the diagnosis of endometriosis and identifying disease behavior in terms of molecular and clinical subtypes, progression potential and susceptibility for specific treatment regimens.

Future perspective

Further efforts should be made to incorporate the relevant determinants and proposed interventions identified in this thesis in a multifaceted strategy aimed at optimizing help seeking behaviour of women with symptoms suggestive of endometriosis, and improving knowledge and clinical strategies in medical professionals. In order to succeed, it is of great importance to join the commitment of all relevant stakeholders in the development of targeted interventions. Scientific programs should not only be aimed at the discovery of new diagnostic or treatment options, but incorporate patients' personal views toward a high standard of medical and personalized care. Besides fundamental research and randomized clinical trials, other study designs including qualitative or mixed method studies will provide important information on opportunities to raise awareness and improve endometriosis care.

Final conclusion

This thesis presents a comprehensive overview of determinants of the diagnostic delay of endometriosis from a multidimensional perspective. The diagnostic process in endometriosis is hampered by late presentation of a diversity of symptoms to a medical professional, inadequate appraisal of symptoms due to insufficient knowledge and the poor interaction between patients and medical professionals. Although the diagnostic delay is a complex phenomenon, multiple opportunities to reduce the interval between onset of symptoms and diagnosis were defined and prioritized by an expert panel consisting of a wide variety of stakeholders. Most importantly, efforts should be made to increase awareness on endometriosis in the general population, and to provide medical staff with sufficient knowledge and skills to adequately acknowledge presented symptoms or clinical findings and initiate appropriate actions in a timely matter.

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Endometriosis is one of the most common benign gynaecologic conditions, with an estimated prevalence of 2-10% in women of reproductive age. It is defined as the presence of endometrial like tissue outside the uterus, which can cause chronic pelvic pain and subfertility. There are three types of endometriosis: peritoneal endometriosis, ovarian endometrioma and deep endometriosis. The clinical appearance of the condition is highly variable, which poses difficulties for clinicians to diagnose the condition in a timely matter. The aim of the thesis is to study all relevant determinants of the diagnostic delay of endometriosis in a multidimensional approach.

Chapter 1 describes the current theories on the pathogenesis of endometriosis, the clinical aspects of reaching a diagnosis and an overview of the literature regarding diagnostic delay of endometriosis, serving as an introduction to the studies presented in this thesis.

In **chapter 2**, the duration of the diagnostic delay of endometriosis in The Netherlands is determined by interviewing 93 women with confirmed endometriosis treated in a hospital with expertise in endometriosis. Median time between onset of symptoms and diagnosis was 89 months or 7.4 years. Diagnostic delay was shorter for women consulting their general practitioner because of subfertility as compared to women with pain or other pelvic symptoms (median delay of 21 versus 100 months, $p=0.024$). Median age of onset of symptoms was 20 years while median age at diagnosis was 31 years. The diagnostic delay consisted of three elements: the interval between onset of symptoms and seeking medical help, also referred to as the patient's delay, the interval between first consultation in primary care and referral to a gynaecologist (the general practitioner's delay), and the time between first specialist consultation and diagnosis (the gynaecologist's delay). The median patient's delay was 7 months, the general practitioner's delay 35 months and the gynaecologist's delay 5 months. The patients' perspective in the diagnostic delay is further elucidated in the qualitative study presented in **chapter 3**. The aim of this study was to identify strengths and weaknesses in the current diagnostic process of endometriosis from the patients' point of view. In this study, 23 women with endometriosis reflected on their own experiences in the diagnostic process in six focus group sessions. Three main themes emerged: 1) knowledge about normal menstruation and endometriosis in both the general population and medical professionals, 2) being believed and acknowledged by medical professionals, and 3) collaboration between health care providers including fast referral to a gynaecologist.

Facilitating factors for a timely referral were a desire for pregnancy, the disclosure of specific symptoms related to the menstrual cycle, and persistence in requesting referral. Suggested interventions to reduce diagnostic delay in endometriosis were directed at increasing awareness in the general population, and providing medical staff (in particular general practitioners) with sufficient knowledge and skills to interpret presented symptoms or clinical findings correctly.

The second part of the thesis starts with a questionnaire study to evaluate the knowledge and clinical strategies of general practitioners in **chapter 4**. The 101 participating general practitioners appeared to underestimate the diagnostic delay of endometriosis, in particular the proportion in primary care. The results of the questionnaire indicated that if the general practitioners considered endometriosis as a possible diagnosis, adequate action was undertaken. However, since the prevalence rate of endometriosis was highly underestimated, they did not seem to recognize the symptoms that may be caused by endometriosis in all women. The focus group study presented in **chapter 5** provides more detailed understanding of barriers and facilitators to a timely diagnosis of endometriosis in primary care. Six focus group sessions, in which 43 general practitioners participated, revealed relevant determinants of practice in four themes: professionals' experience and competence, patient characteristics, guideline factors and professional collaboration. Limited knowledge and awareness and the lack of an appropriate guideline appeared to result in a low priority for establishing the diagnosis of endometriosis. The general practitioners felt that definite diagnosis is not always beneficial, since it may induce a burden of disease or "stigma" to some women. Furthermore, the general practitioners feared the inappropriate use of invasive techniques. Infertility, patient assertiveness and a recent training or serious case were facilitating factors for referral. The general practitioners unanimously preferred more collaboration with gynaecologists about indications and instructions for empirical or first line treatment and timing of referral. They were in favour of the development of a new national guideline in which up to date recommendations with regard to the use of diagnostic tests, empirical treatment and indications for referral to a gynaecologist are provided.

The third part of the thesis is directed at the gynaecologists' view on diagnostic delay of endometriosis. **Chapter 6** presents a nation-wide questionnaire study which focussed on current care performance and gynaecologists' opinion on

the diagnostic delay. The key recommendations from the most recent ESHRE guideline were overall well known; 99-100% of respondents agreed with and 91-100% adhered to the diagnosis-related recommendations in the guideline. Median diagnostic delay was estimated at 42 months by the gynaecologists, which is substantially lower than the delay of 89 months provided by patients. Main factors contributing to diagnostic delay according to gynaecologists are lack of knowledge and awareness of endometriosis in both patients and medical professionals, as well as limitations in diagnostics and late referral. Suggested interventions to reduce diagnostic delay are aimed at improving knowledge and awareness in both patients and medical professionals, as well as improving collaborations between medical professionals.

In the fourth part of the thesis, future efforts to reduce diagnostic delay of endometriosis are discussed in **chapter 7**. Relevant barriers and facilitators from the previous chapters were incorporated into a list of potential interventions to reduce diagnostic delay and presented to an expert panel in a Delphi study. The expert panel consisted of patients (n=26) and professionals (n=55, of which 23 general practitioners, 26 gynaecologists and 6 miscellaneous professionals). They rated and prioritized 36 interventions in four consensus rounds resulting in a set of 10 key interventions. The selected interventions were mainly directed at improving knowledge and awareness in medical professionals by increasing education for medical students, trainees and medical specialists including general practitioners, gynaecologists and other medical specialists encountering women in their reproductive life span (n=7). The other three selected interventions advocate expanding research directed at non-invasive diagnostic tests, the development of a multidisciplinary national guideline concerning menstrual complaints including indications for referral, and the development of a decision aid for the diagnostic process. This set of key interventions is supported by a wide diversity of stakeholders in the field. Analysis of the consensus procedure revealed subgroup preferences for a number of interventions, which although these interventions did not make it to the final selection, they may be of potential interest for improving endometriosis awareness and medical care in specific settings. The results of this study can serve as input for a multifaceted intervention strategy aimed at optimizing help seeking behavior of women with symptoms suggestive of endometriosis, and improving knowledge and clinical strategies in medical professionals.

Finally, the content of this thesis is discussed in a wide perspective in **chapter 8**. The main focus of this chapter is on different point of views on the multiple aspects of diagnostic delay of endometriosis. Furthermore, future perspectives on reducing the delay are discussed.

Samenvatting

Endometriose is een van de meest voorkomende goedaardige gynaecologische aandoeningen, met een geschatte prevalentie van 2-10% bij vrouwen in de vruchtbare levensfase. Endometriose wordt gedefinieerd door de aanwezigheid van endometriumachtig weefsel buiten de baarmoeder, wat kan leiden tot menstruatiepijn, chronische bekkenpijn en onvruchtbaarheid. Er zijn drie types endometriose: peritoneale endometriose, ovariële endometriomen en diepe endometriose. De klinische presentatie van de aandoening is zeer variabel, en dit maakt het vaak lastig om de diagnose vlot te stellen. Het doel van dit proefschrift is om de verschillende determinanten die bijdragen aan het diagnostisch delay bij endometriose vast te stellen vanuit een multidimensionale aanpak.

Hoofdstuk 1 beschrijft de huidige theorieën over de pathogenese van endometriose, de klinische aspecten van het stellen van de diagnose en een overzicht van de literatuur met betrekking tot het diagnostisch delay van endometriose. Dit hoofdstuk dient als algemene inleiding tot de studies die worden gepresenteerd in dit proefschrift.

In **hoofdstuk 2** wordt de duur van het diagnostisch delay van endometriose in Nederland onderzocht door het interviewen van 93 vrouwen met een bevestigde diagnose die worden behandeld in een ziekenhuis met expertise op het gebied van endometriose. De mediane tijd tussen het ontstaan van klachten en het stellen van de diagnose bedraagt 89 maanden of 7.4 jaar. Het diagnostisch delay was korter bij vrouwen die hun huisarts bezochten vanwege kinderwens vergeleken met vrouwen met pijn of andere buikklachten (mediaan delay 21 versus 100 maanden, $p=0.024$). De mediane leeftijd waarop de klachten begonnen was 20 jaar, terwijl de mediane leeftijd bij diagnose 31 jaar was. Het diagnostisch delay bestond uit drie onderdelen: het interval tussen het ontstaan van klachten en het zoeken van medische hulp, ook wel het patiënten delay genoemd, het interval tussen het eerste consult bij de huisarts en verwijzing naar een gynaecoloog (het huisartsen delay), en de tijd tussen het eerste consult bij de gynaecoloog tot de diagnose (het gynaecologen delay). Het patiënten delay bedroeg zeven maanden, het huisartsen delay 35 maanden en het gynaecologen delay vijf maanden. Het perspectief van de patiënt met betrekking tot het diagnostisch delay is verder opgehelderd in de kwalitatieve studie gepresenteerd in **hoofdstuk 3**. Het doel van deze studie was om sterke en zwakke punten in het huidige diagnostische

proces vanuit de visie van de patiënt te identificeren. In dit onderzoek bediscussieerden 23 vrouwen met endometriose hun ervaringen met het diagnostische proces in zes focus groepen. Hieruit kwamen drie hoofdthema's naar voren: 1) kennis over de normale menstruatiecyclus en endometriose bij zowel de algemene bevolking als medisch professionals, 2) erkenning en geloofd worden door medisch professionals, en 3) samenwerking tussen zorgverleners en een snelle verwijzing naar een gynaecoloog. Factoren die een snelle diagnose bevorderden waren kinderwens, het uiten van specifieke klachten gerelateerd aan de menstruatiecyclus, en het aandringen op een verwijzing door de vrouw zelf. Gesuggereerde interventies om het delay te verkorten waren gericht op het vergroten van awareness in de algemene bevolking, en het bevorderen van voldoende kennis en vaardigheden bij medisch professionals (in het bijzonder huisartsen) om de gepresenteerde symptomen of klinische bevindingen correct te kunnen interpreteren.

Het tweede deel van het proefschrift begint met een vragenlijststudie om de kennis en klinische vaardigheden van huisartsen te onderzoeken in **hoofdstuk 4**. De 101 deelnemende huisartsen bleken de prevalentie van endometriose en het diagnostisch delay te onderschatten, in het bijzonder het deel van het delay in de eerste lijn. De vragenlijst wees uit dat huisartsen adequaat handelden als ze endometriose als mogelijke diagnose overwogen. Echter, het feit dat de prevalentie van endometriose fors werd onderschat suggereert dat huisartsen de symptomen veroorzaakt door endometriose bij veel vrouwen niet als dusdanig herkennen. De focus groep studie gepresenteerd in **hoofdstuk 5** verschaft meer gedetailleerde informatie over belemmerende en bevorderende factoren voor het tijdig stellen van de diagnose endometriose in de eerste lijn. Tijdens zes focus groepen, waarin in totaal 43 huisartsen participeerden, werden relevante factoren geïdentificeerd binnen vier domeinen: kennis en competentie van professionals, patiëntkarakteristieken, factoren met betrekking tot richtlijnen, en samenwerking tussen professionals. Beperkte kennis en awareness, en het gebrek aan een geschikte richtlijn leken te resulteren in een lage prioriteit voor het stellen van de diagnose endometriose. De huisartsen waren van mening dat een definitieve diagnose niet altijd bevorderlijk is, aangezien het een ziektelast of "stigma" met zich mee kan brengen. Daarnaast uitten ze de angst voor overmatig gebruik van invasieve diagnostische technieken zoals laparoscopie. Onvruchtbaarheid, patiëntparticipatie en een recente training of ernstige casus kwamen naar voren als bevorderende factoren. De huisartsen waren allemaal voorstander van een betere samenwerking

met gynaecologen, met name op het gebied van instructies voor eerstelijns behandeling en verwijzing. De huisartsen adviseerden het ontwikkelen van een nieuwe landelijke richtlijn waarin up to date aanbevelingen voor diagnostiek, empirische behandeling en indicaties voor verwijzing naar een gynaecoloog worden beschreven.

Het derde deel van het proefschrift richt zich op de visie van gynaecologen op het diagnostisch delay bij endometriose. **Hoofdstuk 6** geeft de resultaten van een landelijk vragenlijst onderzoek weer, gericht op de huidige inrichting van de endometriosezorg in Nederland en de opinie van gynaecologen met betrekking tot het diagnostisch delay. De kernaanbevelingen van de meest recente ESHRE richtlijn waren over het algemeen goed bekend. 99-100% van de ondervraagden was het eens met en 91-100% volgde de aanbevelingen uit de richtlijn die betrekking hadden op diagnostiek. Het diagnostisch delay werd door de gynaecologen geschat op 42 maanden, wat beduidend lager is dan het delay van 89 maanden uit het onderzoek bij patiënten. De belangrijkste factoren die bijdragen aan het diagnostisch delay zijn volgens de gynaecologen een gebrek aan kennis en awareness met betrekking tot endometriose bij zowel patiënten als medisch professionals, evenals beperkingen in diagnostiek en late verwijzing. De genoemde suggesties ter verkorting van het delay waren gericht op een toename van kennis en awareness bij patiënten en hulpverleners, en het verbeteren van samenwerking tussen medisch professionals.

In het vierde deel van het proefschrift worden toekomstige inspanningen om het diagnostisch delay bij endometriose terug te dringen bediscussieerd in **hoofdstuk 7**. Relevante belemmerende en bevorderende factoren uit de onderzoeken beschreven in de voorgaande hoofdstukken werden verwerkt tot een lijst met mogelijke interventies om het delay te verkorten, en voorgelegd aan een expert panel in een Delhi studie. Het expert panel bestond uit patiënten (n=26) en professionals (n=55, waarvan 23 huisartsen, 26 gynaecologen en zes overige professionals). Zij beoordeelden en rangschikten 35 mogelijke interventies in vier consensus rondes, resulterend in een set van 10 geselecteerde interventies. Zeven van deze interventies waren met name gericht op een toename van kennis en awareness bij medisch professionals door uitbreiding van scholing over endometriose voor geneeskundestudenten, arts-assistenten en medisch specialisten, inclusief huisartsen, gynaecologen en andere specialisten die te maken krijgen met vrouwen in de vruchtbare levensfase. De andere drie geselecteerde interventies waren gericht op het uitbreiden van medisch wetenschappelijk

onderzoek naar niet-invasieve diagnostische technieken, de ontwikkeling van een multidisciplinaire landelijke richtlijn over menstruatieklachten inclusief indicaties voor verwijzing, en de ontwikkeling van een keuzehulp om te gebruiken tijdens het diagnostisch proces. Deze set geselecteerde interventies wordt ondersteund door een groot aantal belanghebbenden op het gebied van endometriose. Analyse van de consensus procedure liet zien dat sommige subgroepen van experts in het panel een sterke voorkeur hadden voor bepaalde interventies. Hoewel een aantal van deze interventies de uiteindelijke selectie niet heeft gehaald, kan het van belang zijn om specifieke voorkeuren mee te nemen in toekomstige projecten gericht op verbetering van awareness en kwaliteit van zorg op bepaalde gebieden. De uitkomsten van deze studie kunnen dienen als basis voor een gevarieerde interventiestrategie gericht op het optimaliseren van toegang tot medische zorg voor vrouwen met klachten suggestief voor endometriose, en het verbeteren van kennis en vaardigheden bij medisch professionals.

Tot slot wordt de inhoud van dit proefschrift vanuit een breder perspectief bediscussieerd in **hoofdstuk 8**. In dit hoofdstuk worden de verschillende aspecten van het diagnostisch delay bij endometriose vanuit diverse invalshoeken bekeken, en wordt een toekomstbeeld geschetst met betrekking tot het terugdringen van het diagnostisch delay.

Research data management

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies (File number CMO 2016-2629).

This project is stored on the Radboudumc, department server: (H:) VERLGYNdata\$\(\UMCfs049) under Onderzoek.

In our studies, patients and general practitioners received a questionnaire and the written informed consent prior to the start of their focus group. The hard copies were stored in the department archive (Radboudumc, room M325.01.204), closet number 6. Data management and monitoring were also performed within Castor EDC. An audit trail was incorporated to provide evidence of the activities that have altered the original data. Data were converged from Castor EDC to SPSS (SPSS Inc., Chicago, Illinois, USA).

The patient data for the analyses of the studies as presented in chapter 2 and 3 is stored on the departments' H-drive (H:\VERLGYNdata\$\(\UMCfs049)\Onderzoek\VPG-diagnostic delay endometriosis in SPSS format: Database interview studie patiënten (chapter 2), and in Word format: Focusgroepen patiënt en endometriose\Transcripten (chapter 3). The data for chapter 4, 5, 6 and 7 is stored on the departments' H-drive (H:\VERLGYNdata\$\(\UMCfs049)\Onderzoek\VPG-diagnostic delay endometriosis).

The data will be saved for 15 years after termination of the study (28-03-2017). Using these patient data in future research is only possible after a renewed permission by the patient as recorded in the informed consent. The datasets analyzed during these studies are available from the corresponding author on reasonable request.

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	Year(s)	ECTS	
TRAINING ACTIVITIES			
a)	Courses & Workshops <ul style="list-style-type: none">- Introduction course RIHS- Basiscursus Regelgeving en Organisatie Klinisch onderzoek (BROK) course- Qualitative research methods in healthcare (Care) course- Scientific integrity course	2016 2016 2016 2017	0.5 1.5 1 1
b)	Seminars & lectures <ul style="list-style-type: none">- VPG pijlerdag (oral presentation)- NVOG SIG endometriosis symposia	2018 2016-2018	0.25 0.6
c)	Symposia & congresses <ul style="list-style-type: none">- European Society of Human Reproduction and Embryology (ESHRE) congress München (poster presentation)- Society of Endometriosis and Uterine Disorders (SEUD) congress Paris (oral presentation)- World Endometriosis Society (WES) congress Vancouver (two poster presentations)- European Congress on Endometriosis Vienna (oral and poster presentation)- European Society of Human Reproduction and Embryology (ESHRE) Congress Vienna	2014 2015 2017 2018 2019	0.5 1.25 2.0 2.0 1.0
d)	Other <ul style="list-style-type: none">- journal clubs	2016-2018	0.5
TEACHING ACTIVITIES			
e)	Other <ul style="list-style-type: none">- regional residents research meetings (two oral presentations)- teaching in general curriculum Bachelor students	2016-2018 2017	0.5 0.5
f)	Supervision of internships / other <ul style="list-style-type: none">- Supervision Master student research internship	2016	1.0
TOTAL			14.1

Curriculum Vitae

Moniek van der Zanden werd op 15 maart 1983 als eerste van een tweeling geboren in het VieCuri Ziekenhuis te Tegelen en groeide op in Blerick. Na het cum laude behalen van haar gymnasium diploma aan het Blariacum College van de Scholengemeenschap Venlo, kon zij direct starten met de opleiding Geneeskunde aan de Radboud Universiteit te Nijmegen. Nadat zij in oktober 2007 haar artsenbul behaalde startte zij in januari 2008 als arts-assistent niet in opleiding op de afdeling gynaecologie en verloskunde van het Vlietland Ziekenhuis te Vlaardingen. Vanaf juli 2008 zette zij deze werkzaamheden voort in Ziekenhuis Rijnstate Arnhem.

In oktober 2011 begon Moniek aan de opleiding tot gynaecoloog in het cluster Nijmegen in Ziekenhuis Gelderse Vallei Ede (opleider dr. M.J.N. Weinans), Ziekenhuis Rijnstate Arnhem (opleider dr. F.P.H.L.J. Dijkhuizen) en het Radboudumc (opleiders dr. R.L.M. Bekkers en dr. A.C. Bolte). Tijdens het derde jaar van de opleiding werd een start gemaakt met het onderzoek wat heeft geleid tot dit proefschrift. De laatste twee jaar van haar opleiding stonden in het teken van differentiatiestages op het gebied van voortplantingsgeneeskunde en benigne gynaecologie.

Op 27 december 2018 rondde Moniek haar opleiding tot gynaecoloog met succes af. Hierna werkte zij als chef de clinique in Ziekenhuis Gelderse Vallei Ede. Per 1 augustus is zij gestart als gynaecoloog in Haaglanden Medisch Centrum in Den Haag. Zij voltooide haar promotietraject naast haar opleiding en klinische werkzaamheden.

Sinds 2004 is Moniek samen met haar partner Huub. Samen hebben zij twee prachtige kinderen: Lotte (2013) en Lukas (2016).

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