Medical Hypotheses 82 (2014) 493–501

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Clinical markers of endometriosis: Have we been too quick to judge?

K. Toor [a], J.M. Wessels [a], S.K. Agarwal [b], N. Leyland [a], W.G. Foster [a,*]

[a] Department of Obstetrics & Gynecology, McMaster University, Hamilton, Ontario L8S 4K1, Canada
[b] Department of Reproductive Medicine, University of California San Diego, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:
Received 28 October 2013
Accepted 5 February 2014

ABSTRACT

Numerous biochemical differences have been documented in women with endometriosis compared to controls; however, identification of a clinically useful marker of endometriosis remains elusive. We postulate that the diversity of clinical presentations, patient objectives, and complexity of the pathophysiology of endometriosis mandates rigorous attention to study design and standardization of procedures and questionnaires that has heretofore been overlooked in the pursuit of clinical markers of this enigmatic disease. We further propose that it is premature to conclude that clinical markers of endometriosis brought forward in the literature lack clinical value in the diagnosis of endometriosis. To address this hypothesis we reviewed the literature and assessed papers according to a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria from which 55 high quality papers were reviewed. While pelvic inflammation and pain is a known significant component of endometriosis, control group definitions were widely divergent and included healthy women through to women with other inflammatory conditions. Although pain is a common presenting complaint in women with endometriosis, it was assessed in only 4 of 55 studies (7.3%) whereas infertility was documented in 34/55 studies (61.8%). Disease severity was assessed in 44 of 55 studies (80%) whilst the association between active vs. inactive disease was attempted in only 2 of the studies reviewed (3.6%). We conclude that experimental design criteria are inconsistently applied making comparisons across studies difficult. Thus, the clinical utility of previously described diagnostic markers of endometriosis remains uncertain.

Introduction

Endometriosis is a gynecological disease of unknown etiology characterized by growth of endometrial stroma and glands in extra-uterine sites [1]. It is a chronic estrogen dependent inflammatory condition with a prevalence that varies according to population studied and ranges from up to 7% of women in the general population, 30% of women with chronic pelvic pain, and 50% of infertile women [2–5]. Women with endometriosis report significant pain during menstruation and intercourse, leading to health distress and interference with normal activities during work and leisure time [6]. In addition to pain and infertility, endometriosis has a deleterious effect upon women's social functioning, emotional well-being, relationships with medical practitioners, vitality, and employment [7]. The total economic costs associated with caring for women with endometriosis are estimated to be approximately 1.8 billion dollars in Canada [8], an amount similar to or greater than the costs associated with other chronic conditions such as migraine, Crohn's disease, diabetes, asthma and rheumatoid arthritis [9].

A significant obstacle in understanding the pathophysiology and treatment of endometriosis is the lack of a diagnostic test specific for this disease. While numerous biochemical differences have been documented in women with endometriosis versus disease free controls [10–13], none have been found to be specific for endometriosis. Chief among the difficulties facing physicians attempting to diagnose endometriosis are: early age at onset of symptoms, normalization of pain by primary care providers, and hormonal suppression of symptoms through intermittent use of contraceptives [14,15]. As a result women with endometriosis experience delays of up to 12 years in diagnosis [9,16] and thus access to appropriate treatment is also often delayed [1] leading to significant avoidable morbidity. We also suggest that endometriosis is a complex disease affecting women from a wide range of ages and divergent reproductive needs. In women who do not wish to become pregnant, medical management of symptoms through estrogen suppression is generally the first line therapy. However, management is more complex for women trying to become pregnant. Hence, these factors require careful consideration during

* Corresponding author. Address: HSC-3N52D, Department of Obstetrics & Gynecology, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4K1, Canada. Tel.: +1 (905) 525 9140x22822; fax: +1 (905) 524 2911.
E-mail address: fosterw@mcmaster.ca (W.G. Foster).

http://dx.doi.org/10.1016/j.mehy.2014.02.007
0306-9877/

the study design stage and standardized inclusion and exclusion criteria should be used. Moreover, duration of illness, burden of disease, lesion activity, location of lesions, concomitant hormone treatment, severity of disease, menstrual cycle stage, and age are all potentially important modifiers of clinical marker measurements. We postulate that failure to adequately account for the above factors could seriously compromise efforts to identify clinically useful markers of endometriosis. Therefore, identification and careful characterization of novel clinical markers of endometriosis remains a high priority.

Endometriosis is presumptively diagnosed through assessment of patient history, signs and symptoms, and imaging studies. However, the gold standard for diagnosis remains visualization of endometriotic lesions, typically by laparoscopy followed by histopathological confirmation of disease. The disease is staged during laparoscopy according to the revised American Fertility Society (rAFS) classification system [17]. This classification system is based on the location and extent of lesions and classifies the disease into four stages including minimal, mild, moderate, and severe. However, a limitation of this classification system is that stages relate poorly to pain and infertility. Alternatively, endometriosis can be classified on the basis of lesion appearance as red, black or bluish, and white lesions [18]. Red and black or bluish lesions are thought to represent active disease whereas white lesions are considered inactive. While many prior studies have examined the relationship between disease severity and concentrations of clinical markers, we postulate that the relationship between active vs. quiescent lesions could help explain variation in clinical marker measures and the reported lack of suitable sensitivity, specificity, and predictive value [10–13].

A plethora of potential clinical markers for the diagnosis of endometriosis have been brought forward in the literature. Of the myriad of biomarkers identified to date, several have received more research attention than others and include: cancer associated protein 125 (CA125), vascular endothelial growth factor (VEGF), and several interleukins such as IL-6 and IL-8 [19–31]. In recent years, nerve fiber density in the endometrium [32,33], concentrations of neurotrophins in the endometrium [34] or circulation [35], and measurement of microRNA (miRNA) in endometrial biopsies and endometriotic lesions [36,37] has been proposed as potentially useful diagnostic markers of endometriosis. Unfortunately, no clinical marker of endometriosis has been found to have adequate sensitivity, specificity, or predictive value to be used as diagnostic marker of endometriosis [10–13]. Hence, the search for novel clinical markers of endometriosis remains a high priority. Therefore, we undertook a review of the literature to elucidate current approaches in study design and to identify best practices to guide future studies aimed at characterizing novel diagnostic makers of endometriosis.

Methods

We conducted a review of the literature between May and July 2013, focused on reports of clinical markers of endometriosis using PubMed, MEDLINE, EMBASE, and CINAHL. Abstracts were reviewed and studies in humans designed to assess the utility of clinical markers of endometriosis were identified. The abstracts were reviewed by two independent reviewers (KT and WGF). Studies were subsequently assessed according to a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria Table 1. All studies were given pass/fail grades in eleven categories. For the purpose of this review, category seven (“Was the diagnosis of endometriosis made without the knowledge of the biomarker test results?”) was excluded in our analysis as it was marked as unclear for all the studies. For the purposes of the present review, we only included studies that scored six out of 10 or higher on the QUADAS criteria consistent with prior biomarker reviews [10,11]. The selected studies ($n = 55$) were reviewed to elucidate the criteria used to define cases vs. controls and methods used to assess patient pain and quality of life in cases and control subjects. The reference lists were also searched to identify studies missed using our search strategy. Furthermore, in view of the estrogen dependent nature of endometriosis and role of gonadal steroids in regulating the expression of proteins central to the pathophysiology of this disease, we determined the hormone free interval before entrance into a study. We also evaluated whether clinical markers were characterized according to menstrual cycle stage, or associated with disease severity, and/or type of lesion (red, blue-black or white lesions).

Results

The importance of surgical confirmation of endometriosis is well recognized and laparoscopy was used in 48 of the 55 studies examined (87.3%) to distinguish between cases and controls Table 2. However, there is a lack of consensus in the literature concerning the definition of appropriate controls. Definition of control groups varied widely between studies and included women undergoing tubal ligation [19], women with unexplained infertility [38], women with ovarian or para-tubal cysts [27], healthy women with previously documented fertility [39], women with benign tumors [40], and women with benign ovarian cysts and healthy women with regular menstrual cycles [41]. In one study cases served as their own control [42] and in another study males undergoing thoracic surgery were used as the comparison group [23].

Of the 55 studies reviewed, 32 (58.2%) reported a positive association between the clinical marker of interest and endometriosis but statistical significance was achieved in only 17 (30.9%) of these studies [22,24,41,43–56] although low sensitivity and specificity has frequently been reported. In addition to a dichotomous response of being able to diagnose the presence or absence of endometriosis, correlation of the clinical marker with disease severity is desirable. In the papers that we reviewed, the relationship between the clinical marker and severity of disease was described in 44 of 55 papers (80%) using either the AFS or rAFS system for staging disease. We also postulated that the relationship between the clinical maker of endometriosis and type (red, blue-black or white) or location of the lesion may enable stratification of study results that could improve clinical marker sensitivity, specificity and predictive values. However, the type of lesion was reported in only 2 of the 55 studies (3.6%) reviewed [24,57].

Chief among the presenting complaints for women with endometriosis are infertility and pain. In our review of the highest quality papers seeking to identify a clinical marker of endometriosis, fertility status was not reported in 34 of 55 papers (61.8%) but was cited as the indication for surgery in 17 papers (30.9%). By comparison, pain was evaluated in only 4 of the 55 studies (7.3%) reviewed.

Endometriosis is frequently managed using hormone therapies such as oral contraceptives, androgenic agents, and gonadotropin releasing hormone (GnRH) antagonist, all of which could affect expression and circulating concentrations of the clinical markers of interest. While a washout period is recognized as an important requirement before being enrolled into an endometriosis study, the requirements for a hormone free interval and length of interval is ambiguous. In 20 of the 55 papers reviewed (36.4%), the use of hormonally active therapies or the drug free interval were not specified. In the studies that provided information on the hormone free interval, there was marked inconsistency in the length of time with 3, 6, and 12 month intervals reported Table 2.