Non-invasive diagnosis of endometriosis: the goal or own goal?

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ABSTRACT: Laparoscopy is the gold standard for the diagnosis of endometriosis. Although some forms of the disease, such as ovarian endometriomas or deep infiltrating lesions, can now be reliably diagnosed using non-invasive instruments, adhesions and superficial implants cannot be identified without surgery. Identification of these latter forms of the disease has been the main rationale for claiming the necessity to identify non-invasive diagnostic tests to detect endometriosis. In this opinion paper, we analyse the pros and cons of the availability of this kind of test in the current context of our knowledge of the disease. In particular, we emphasize that this instrument may be of benefit provided that the test is not used as a screening test.

Key words: endometriosis / diagnosis / screening / disease mongering

Introduction

There is a general consensus that laparoscopy is the gold standard for the diagnosis of endometriosis. It allows direct visualization of the lesions and histological confirmation (Farquhar, 2007; Bulun, 2009). Unfortunately, laparoscopy is a costly invasive procedure requiring general anaesthesia and it is inevitably associated with rare but potentially severe complications (Chapron et al., 2002; Vercellini et al., 2009a). For this reason, efforts are now aimed at identifying non-invasive diagnostic tests to detect endometriosis. A consensus workshop, convened following the 10th World Congress on Endometriosis, concluded that this is one of the main priorities in endometriosis research (Rogers et al., 2009).

Imaging for endometriosis

Fortunately, some forms of the disease can now be accurately diagnosed prior to surgery. A consistent body of literature supports the accuracy of transvaginal ultrasound for the detection of ovarian endometriomas. Sensitivity and specificity of this method have been reported to be 84–100% and 90–100%, respectively (García-Velasco and Somigliana, 2009; Savelli, 2009).

Detection of deep infiltrating lesions is however more challenging. Several imaging methods, such as transvaginal ultrasonography, transrectal ultrasonography, computerized tomography and magnetic resonance imaging (MRI) have been used in an attempt to improve the non-invasive diagnosis of this form of endometriosis (Abrao et al., 2007). Most evidence is focused on the rectal and utero-sacral ligation localization, since they are the most common. Comparative studies are scarce and inconsistent. In general, however, transvaginal ultrasonography seems to be at least as accurate as the two other approaches while being more accessible and less inconvenient. The sensitivity and specificity of the technique is 78–98% and 90–100%, respectively (Abrao et al., 2007; Bazot et al., 2007, 2009; Piketty et al., 2009). Conversely, MRI may be more reliable for vaginal and extra-pelvic localizations (Bazot et al., 2009).

While important progress has been made during the last two decades for the non-surgical diagnosis of ovarian and deep infiltrating endometriosis, efforts aimed at identifying adhesions and superficial implants prior to surgery have until now led to disappointing results. Difficulties in the detection of these latter forms of the disease have lead to the claims that finding new non-invasive diagnostic tests for endometriosis is a necessity.

From diagnosis to screening

A diagnostic test is defined as the application of a variety of examinations or tests to patients who have actively sought health-care services in order to identify the exact cause for their complaints. In contrast, screening is the systematic application of a test or enquiry to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action amongst
persons who have not sought medical attention on account of symptoms of that disorder (Wald, 2001). The distinction between the two is thus whether or not that individual would have sought service for that particular problem (Peters et al., 1996).

This is a crucial point for women with endometriosis. At present, physicians typically prescribe tests aimed to identify endometriosis in women complaining severe pelvic pain or subfertility. The most typical patients are those with unexplained severe pelvic pain refractory to non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives and those seeking pregnancy for more than 1 year with unremarkable preliminary infertility tests. Endometriosis is common in these cases and the identification of the disease may guide therapeutic decisions. The availability of a reliable non-invasive test to detect the disease would thus help to avoid worthless diagnostic laparoscopies (Catenacci et al., 2009; Vercellini et al., 2009a, b).

On the other hand, the limit that moves women forward to actively sought health-care services is not rigid and may vary. The availability of a simple test able to detect endometriosis is expected to shrink this limit and to boost the demand for the test. The ultimate effect would be to increase the number of women who are diagnosed with the disease. In this context, it is first wise to note that awareness of endometriosis is currently spreading in the general population. More and more women are becoming aware of its existence. In Italy, the Minister of Health has supported a promotional campaign in the media aimed at increasing disease awareness and advocating the need for early diagnosis (www.quellochenonsodime.it) (Bianconi et al., 2007).

Secondly, some typical symptoms of the disease such as dysmenorrhea or subfertility are common in women of reproductive age. On this basis, a consistent proportion of women may be interested in ruling out endometriosis. There is a very real possibility that a non-invasive diagnostic test aimed at detecting endometriosis in a very specific symptomatic population may, in fact, become a screening test. Potentially interested individuals may include teenagers with dysmenorrhea (regardless of the severity), adolescents with any kind of menstrual morbidity, women in their initial stages of seeking children or even women who are not yet planning a pregnancy but who are interested in assessing their fertility status. Thus, although the medical community might have not intended to introduce a test as a screening test, there is the strong likelihood of its conversion into ‘a non-formal screening’. We would like to invite to a more in-depth reflection on this point since there are enormous differences between a diagnostic and a screening tool and the scientific and clinical community involved in endometriosis cannot be found unprepared for this possible scenario.

### Screening rules: does endometriosis fit the model?

The main criteria for an effective screening for endometriosis (Peters et al., 1996; Massad, 2008) and the relative degrees of satisfaction are synthetically reported in Table I and discussed below. Collectively, the available data do not support the view that this disease would currently benefit from a screening program. Only four out of eight characteristics are satisfied, of which only one is clearly well satisfied.

### Health relevance

Endometriosis is associated with pelvic pain and infertility, which can impact on the physical, mental and social well being of a woman and can have a profound effect on her quality of life, including the ability to finish an education, maintain a career or to bear children (Bianconi et al., 2007). The endometriosis-associated costs to society, including delayed diagnosis and ‘hit-and-miss’ treatments, are considerable but yet poorly identified, as are the costs to the individual when disease symptoms interfere with day-to-day life at work or at home (Gao et al., 2006a). The mean time interval between first symptoms and diagnosis has been reported to be 7–10 years (Hadfield et al., 1996; Dmowski et al., 1997; Husby et al., 2003; Ballard et al., 2006; Matsuzaki et al., 2006). This delay is highly dependent on surgical access (women with less surgical access are less likely to be diagnosed and treated for endometriosis) (Greene et al., 2009) and causes significant morbidity (physical and psychological) for women (Gao et al., 2006a). On the basis of a review of cost estimates, the annual costs of endometriosis were estimated to be 22 billion in 2002 in the USA (Simoens et al., 2007).

Despite this significant health burden, endometriosis remains a benign condition. Whilst it is well-accepted that endometriotic lesions may evolve into cancer, the frequency of this event is rare. The clinical relevance of this risk and the therapeutic implications are therefore controversial (Somigliana et al., 2006; Viganò et al., 2007; Nezhat et al., 2008; Vercellini et al., 2009c). Of relevance here is that the results of epidemiologic studies indicate a mild association with ovarian cancer, with relative risks between 1.3 and 2 being the most frequent finding (Somigliana et al., 2006). This means that, in the worst scenario, the lifetime probability of developing ovarian cancer increases from 1/100 to 2/100. It is also wise to note that nulliparity and infertility, two conditions frequently associated with endometriosis, are both risk factors for this cancer (Jensen et al., 2008; Permutt-Wey and Sellers, 2009). Unfortunately, studies on the association of endometriosis with cancer are not systematically controlled for parity, and never for infertility. Collectively, these data support the view that an association with cancer is plausible but the magnitude is mild (Vercellini et al., 2009c).

### Acceptability of the disease

Endometriosis is a condition of menstruation and infertility that are both commonly taboo topics in society. This disease is poorly recognized and therefore flies under the radar in terms of acceptability in society (Lunenfeld et al., 2004). There is evidence that 50% of women with endometriosis are bedridden for 17.6 days per year, potentially impacting on education and career (Kjerulff et al., 1996). Moreover, sexual dysfunction due to dyspareunia can disrupt relationships for men and women (Gao et al., 2006b). Of utmost relevance here is the association of the disease with infertility. This condition is well-known to undermine women’s quality of life (Dyer et al., 2002). This may be even more relevant in countries of the developing world where infertility is socially extremely shameful and a diagnosis of endometriosis may consequently lead to social stigmatization. In fact, in many developing countries, women who are unable to bear children are rejected by their husbands and ostracized by society, often leaving as outcasts and perceived as inferior and useless (Lunenfeld et al., 2004).
Table 1  Main desirable characteristics of a screening test and degree of satisfaction for endometriosis.

<table>
<thead>
<tr>
<th>Items</th>
<th>Explanation</th>
<th>Degree of satisfaction</th>
</tr>
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<tbody>
<tr>
<td>1. Health relevance</td>
<td>Is the condition an important health problem (significant risk of mortality or morbidity)?</td>
<td>++</td>
</tr>
<tr>
<td>2. Acceptability of the disease</td>
<td>Is the disease acceptable in the population?</td>
<td>-</td>
</tr>
<tr>
<td>3. Natural course</td>
<td>Does the condition have a recognizable latent or early symptomatic phase?</td>
<td>-</td>
</tr>
<tr>
<td>4. Acceptability of the test</td>
<td>Is the test (and its consequences in terms of further diagnostic testing and subsequent treatment) acceptable to the population?</td>
<td>+</td>
</tr>
<tr>
<td>5. Effectiveness of treatment</td>
<td>Is early treatment of the condition effective? Does diagnosis of the disease before symptoms occur results in better outcome than waiting for symptoms?</td>
<td>+</td>
</tr>
<tr>
<td>6. Consensus</td>
<td>Does a consensus exist regarding proper management of abnormal test results?</td>
<td>- -</td>
</tr>
<tr>
<td>7. Complication balance</td>
<td>Is the risk of complication from the test and subsequent evaluation and treatment lower than the risk of morbidity and mortality from the disease?</td>
<td>+</td>
</tr>
<tr>
<td>8. Cost-benefits balance</td>
<td>Are the costs of testing and treating asymptomatic disease acceptable? Do the objectives of the program justify the costs?</td>
<td>+/-</td>
</tr>
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Adapted from Peters et al. (1996) and Massad (2008).
A five-points scale was used to evaluate the degree of satisfaction. It is as follows: not at all (− −), mainly unsatisfied (−), unclear (+/−), partly satisfied (+) and satisfied to a large extent (+ +). Judgement was independently done by all the authors and a consensus was reached by discussion if controversies emerged.

Natural course

The natural course of endometriosis has yet to be understood. Studying this aspect of the disease is difficult because of the need for repeated laparoscopies. Despite the paucity of evidence, there is the widespread belief that endometriosis is a progressive disease. The main aspects supporting this view are the rarity of the diagnosis in adolescence (Eskenazi and Warner, 1997) and disease relapse after surgical removal (Guo, 2009). Both arguments are however somehow debatable. First, the aforementioned delay of several years between the onset of symptoms and diagnosis of the disease may in part explain the infrequency of the diagnosis of endometriosis in adolescents. In other words, endometriosis may simply be under-diagnosed in this group of women. Secondly, at least in some cases, the tendency of the disease to relapse may be due to incomplete treatment. Medical therapies render endometriotic implants quiescent but they do not eradicate them. Surgery may be difficult in women with endometriosis, and there are some concerns that removal of the lesions may frequently be incomplete, in particular in insufficiently experienced hands (Catenacci et al., 2009; Vercellini et al., 2009a, b). Moreover, since surgery does not remove the causes of the disease, recurrences must be expected.

Of further interest here is that the few available observational data do not support the view that endometriosis is a progressive disease. In fact, it has been shown that endometrial deposits may resolve spontaneously. Two studies in which laparoscopy was repeated after treatment in women given placebo reported that, over 6–12 months, endometrial deposits resolved spontaneously in up to a third of women, deterioriated in nearly half, and were unchanged in the remainder (Sutton et al., 1997; Abbott et al., 2004). Moreover, one study focusing on deep rectovaginal endometriotic nodules showed that these lesions are progressive in fewer than 10% of cases (Fedele et al., 2004). Of utmost interest here is that menstrual reflux is a common occurrence (Vigano et al., 2009) and small endometriotic implants are believed to occur frequently in asymptomatic women of reproductive age. Consequently, some of what has been labelled pathologic may instead represent the temporary phase of a normal, ongoing process of cytolysis of recently implanted endometrial fragments (Vercellini et al., 1992; Thomas, 1996; Holt and Weiss, 2000).

Acceptability of the test

Acceptability of the test first refers to whether it is acceptable to patients in terms of pain, fear and inconvenience. As we are debating a theoretical non-invasive diagnostic tool such as blood test, we might assume that acceptability would not be an important concern. This may, however, not be entirely true. In fact, promising results on the use of endometrial biopsies to identify the disease have recently been reported (Al-Jefout et al., 2009; Zhang et al., 2009). If this test were to enter clinical practice, its use may determine some problems of acceptability. Secondly, acceptability also refers to costs. The relevance of this aspect is difficult to foresee. In this paper, we assume that this may not be a relevant concern, while admitting that this may not be entirely true. The third aspect of acceptability refers to consequences in terms of further diagnostic testing and treatment. In our view this is the most troublesome aspect. The diagnosis of endometriosis may be psychologically distressing for women and the subsequent misuse of health-care resources may be an important concern. Once women are diagnosed with the disease, they could be left with a generic diagnosis without the knowledge for discriminat-
there may also be an increase in the number of unnecessary surgical interventions.

**Effectiveness of treatment**

Treatment of endometriosis remains a highly debated topic whose in-depth discussion is beyond the scope of the present contribution. Many comprehensive reviews have been published on this issue (Fedele et al., 2008; Catenacci et al., 2009; Guo, 2009; Vercellini et al., 2009a, b). However, in this context, some points deserve consideration. Surgery is the most effective treatment of the disease, but does not prevent recurrences. The reported recurrence rate is high, estimated as 20% at 2 years and 40–50% at 5 years (Guo, 2009).

As mentioned previously, there are two likely explanations. First, surgery may be incomplete and recurrences are in fact persistent cases due to inadequate primary treatment. Secondly, surgery removes the lesions, but it does not act on the causes of the disease. On this basis, we postulate that identifying endometriosis earlier may lead to an increase in the number of interventions without substantially improving the course of the disease.

In the context of long-term management of women with the disease, hormonal medical treatment may be more appealing. These treatments have been shown to improve pain symptoms. Unfortunately, their effect is limited to the period of assumption and pain typically resumes after discontinuation. Long-term administration of these agents may overcome this limit and may be a feasible option. In line with this view, recent data support a highly effective role of long-term post-surgical administration of oral contraceptives or progestins in the tertiary prevention of the disease. Combining the results from three recent studies on this point, the common odds ratio for the recurrence of ovarian endometrioma and pain in oral contraceptive users is 0.12 (95% CI: 0.03–0.42) and 0.38 (95% CI: 0.22–0.66), respectively (Seracchioli et al., 2008; Vercellini et al., 2008; Takamura et al., 2009). However, even though lower rates of pain recurrences may indirectly suggest a benefit for peritoneal implants and adhesion as well, this aspect has yet to be clarified. Moreover, it remains to be demonstrated whether the beneficial effects in terms of post-surgical tertiary prevention can be extrapolated to unoperated women with mild forms of the disease.

**Consensus**

Consensus regarding proper management of abnormal test results is a critical issue. Introducing a test prior to having clarified this aspect may have a devastating impact on the population. Unfortunately, this issue is far from clear at present. Despite the recent evidence supporting, the beneficial role of oral contraceptives or progestins in the management of the disease, the majority of gynaecologists engaged in this field remain convinced that surgery is the gold-standard of treatment in all the cases. In fact, the debate is yet unresolved and possibly irresolvable due to lack of evidence. Owing to the inability to identify some forms of the disease (adhesions and superficial implants in particular) prior to surgical diagnosis, no study has been able to compare the beneficial effects of surgery versus medical treatment initiated during the latent phase of the disease. In this regard, a benefit of a non-invasive test to detect endometriosis would be to allow this kind of study to take place. Long-term studies following women for several years are required to conclusively resolve this point.

**Complication balance**

On the basis of the hypothesized non-invasive nature of the test, we herein state that the complications from the test are null. Conversely, the risks associated with subsequent evaluation and treatment are possible matters of concern. According to a recent meta-analysis, the rate of major and minor complications associated with laparoscopy is 1.4–7.5%, respectively (Chapron et al., 2002). Medical treatment using oral contraceptives or progestins may be less risky but, given the necessity for long-term administration, compliance is a potential problem. A high rate of drop-out with hormonal therapies is well-documented (Vercellini et al., 2008). This rate may be even higher in women who are asymptomatic. Last, but not the least, the psychological consequences and the impact on the quality of life of being classified as ‘ill’ are difficult to quantify, but is likely to be relevant and should be included in the complications of the test.

Overall, the rate of complications of the test and subsequent evaluations and treatment are not null. Determination of the balance of the pros and cons is difficult due to the lack of precise data. However, taking into consideration the significant morbidity associated with endometriosis, the balance would probably be in favour of a screening test.

**Cost-benefits balance**

In the current climate of growing concerns regarding the economic aspects of health-care, the balance between costs and benefits is fundamental in deciding to implement a screening test. First, the costs of the test and the costs of the treatment (laparoscopy or medical drugs) are not unique points of expense to be considered. Further aspects to be included in the analysis comprise the necessity of developing facilities for confirming the diagnosis and for adequate treatments, the complications of the therapies and the impact on the quality of life of women found to be positive by such a test. In particular, this latest point cannot be properly quantified a priori. A survey following the introduction of such a test would be necessary. On the other hand, and of utmost importance, the benefits cannot currently be estimated. As mentioned above, the proper treatment to prevent endometriosis is debated and there is no clinical evidence regarding the effectiveness of treatment options administered in the latent phase of the disease.

**Final comment**

‘Disease mongering’ is the promotion of sickness that widens the boundary definitions of illness in order to grow markets for those who sell and deliver treatments or diagnostic tests. It is a process that turns healthy people into patients, causes iatrogenic harm (both physical and psychological), and wastes precious resources (Moynihan et al., 2008). In the field of endometriosis, the availability of a non-invasive test for its diagnosis may pose a risk of disease mongering for at least two reasons. First, the disease is common. Epidemiological studies estimate a prevalence of 6–10% (Farquhar, 2007; Bulun, 2009) but this rate may be much higher if milder forms of the disease, which are presently under-diagnosed, are included. A diagnosis of endometriosis can thus be perceived by women as a realistic possibility. Secondly, typical symptoms of the disease are common yet significant concerns for women in their reproductive years. The majority of
women of this age report dysmenorrhea, at least in its milder form. This common, inconvenient but not dangerous condition may thus be reclassified as a health concern. Moreover, due to social constraints, women in the developed world increasingly postpone childbearing to an age when natural female fertility is in decline. They are thus generally concerned about their fertility status, even before attempting to become pregnant, and they may be interested in clinical tests that provide information on their potential fertility.

However, these considerations remain speculative. Predicting the future is an arduous and hazardous task. Some assumptions made in this paper are inevitably theoretical. Of particular relevance here is the characteristics of the population to be tested. The balance between the pros and cons of a non-invasive test for endometriosis is highly dependant on this. We can postulate different scenarios ranging from a general screening for the entire population of reproductive-age women to exclusive use in a highly selected group of women with unexplained subfertility or unexplained severe pelvic pain. The former is hopefully unrealistic. An intermediate situation where such a test is prescribed also to women with non-severe pain symptoms or to those in the initial stages of seeking children, is more plausible and needs in-depth reflection. In this scenario, the limits of inclusion will be wider and the population tested larger. In such a situation, the balance may tip to the cons side. The number of women diagnosed with endometriosis would increase, as would the number of unnecessary laparoscopies and the overall costs for society. In contrast, should the test remain mostly prescribed to the highly selected group of women with unexplained subfertility or unexplained severe pelvic pain, the balance would favour the pro arguments. The delay between symptoms emergence and diagnosis would shorten and the number of unnecessary laparoscopies would drop.

In conclusion, identifying non-invasive tools for the diagnosis of endometriosis is a priority and we consider it to be an important goal which we hope will be fulfilled in the near future. Such a discovery would be of great benefit. We simply hope to issue a warning to the clinical community of the possible consequences of developing such a test. Scientific progress has not systematically translated into health improvement. Researchers should be aware that the identification of a non-invasive test for the diagnosis of endometriosis may be harmful if its use is not properly managed. International Societies should also provide clear indications guiding current research and, in the future, clinical applications. In our view, non-invasive test is for the diagnosis of endometriosis should remain indicated (and used) in the only two groups of women who may benefit from the diagnosis: those with unexplained subfertility and those with unexplained severe pelvic pain refractory to oral contraceptives and NSAIDs.

**References**


