The relevance of asymptomatic endometriosis

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Asymptomatic endometriosis is likely to be a physiological phenomenon of very limited relevance to both the physician and the patient. The evolution of our understanding of this phenomenon is a parable for modern medicine. It is likely that access to a new diagnostic technique, a powerful armoury of medical and surgical treatments and the necessity for doctors to feel they are doing something positive for the patient, have created an incorrect disease model for asymptomatic endometriosis. As responsible clinicians and medical scientists it behoves us to honestly re-examine our approach to this phenomenon.

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Introduction

Twenty years ago discussions about the relevance of asymptomatic endometriosis would have been unnecessary for practising gynaecologists. This was because the diagnosis of endometriosis was only verified by laparotomy and therefore the patient had to be experiencing severe symptoms or have a large pelvic mass before such an intervention would be considered. It is the introduction of the laparoscope which has precipitated the debate as we can now visualise the pelvis easily and often so do in women with no symptoms. Here I will examine the evidence that all endometriosis represents a disease or whether some is physiological and will discuss whether the increasingly frequent finding of asymptomatic endometriosis represents a true change in a disease type or is simply the result of access to a new diagnostic technique. I will then discuss whether asymptomatic endometriosis is a disease that requires treatment and conclude with my opinion about the relevance of asymptomatic endometriosis. Finally I will discuss why medical practitioners may be resistant to accepting that asymptomatic endometriosis is a phenomenon for which treatment is unnecessary. It is not my aim to write this as a referenced article and it is very much a reflection of my own opinion (Thomas, 1993, 1995). However I hope it will be thought-provoking and thus initiate debate.
Is some endometriosis physiological?

In my version of the Compact Edition of the Oxford English Dictionary, physiology is defined as: ‘the science of normal functions and phenomena of living things’. Therefore to conclude that some endometriosis is physiological it must be considered as a normal phenomenon that can explained by normal biological processes.

The pathogenesis of endometriosis is unproven but there is good evidence that the incidence of the phenomenon is related to exposure to menstruation. Endometriosis is more common in women with short menstrual cycles and in those with periods lasting >7 days. It increases in incidence with age which could reflect increasing exposure to menstruation. The oral contraceptive, which decreases menstruation by ~50% protects against endometriosis. Lastly pregnancy, which interrupts consistent exposure to menstruation also protects against endometriosis. Conversely, infertility is a risk factor for endometriosis and this may reflect the fact that infertile women have had little or no exposure to pregnancy and therefore more consistent exposure to menstruation. It is, therefore, logical to conclude that endometriosis is causally related to exposure to menstruation and we would all accept that menstruation is a physiological event.

The next discussion covers the biological mechanisms whereby menstruum may become endometriosis. There is now little doubt that menstrual endometrium flows retrogradely down the Fallopian tubes. It is a common finding at laparoscopy in menstruating women and peritoneal dialysate becomes bloodstained in women during menstruation. It has been demonstrated that refluxed menstruum contains viable cells by culturing tissue collected in a cervical cap during menstruation. Recently endometrial fragments collected from peritoneal fluid have also been successfully cultured in vitro. There is a extensive literature that shows that endometrium can implant in ectopic sites in the animal model. There is less evidence for this in the human, although endometrium was demonstrated to implant in surgical wounds in the abdominal wall in human volunteers some years ago. In both the animal and human models the implantation was of normal, not abnormal, endometrium. Whilst this may limit the value of the model it clearly shows that normal endometrium can implant. In conclusion it is physiological for menstruum to appear in the pelvis, it contains viable cells and it is physiological for those to implant.

Having shown that implantation of refluxed menstruum is physiological, it is important to explore the evidence that this is the pathogenesis of what we understand as endometriosis. There is now a substantial body of literature that reports morphological similarity between endometriosis and endometrium, similar expression of steroid and growth factor receptors, equivalent expression of cytoskeletal proteins and epithelial antigens and similar behaviour in culture. Evidence also exists that peritoneal mesothelium does not have important molecular structures which would enable it to respond to steroid stimulation. Whilst none of this proves that implantation is the mechanism and there is evidence that shows endometriosis without endometrium, it strongly supports the
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paradigm that endometrium is the tissue of origin of endometriosis. If this paradigm is accepted then it is logical that implantation of endometrium is the common mechanism of pathogenesis.

Although not necessary, it is usual for us to consider that for a phenomenon to be physiological it must be shown to have a significant prevalence in the population. This would have been a strong argument against endometriosis being physiological until recently. However there is an increasing incidence of the visual diagnosis of endometriosis at laparoscopy and it was recently reported to be present in 80% of infertile women. Histological evidence of endometriosis can be found in up to 15% of biopsies of normal peritoneal mesothelium. I believe that these data mean that some endometriosis is a common phenomenon in pre-menopausal adult women which may be ubiquitous or may wax and wane throughout their reproductive career.

I conclude, therefore, that there is considerable evidence to suggest that visible endometriosis is the result of implantation of refluxed normal menstrual endometrium. It is likely that small amounts of endometriosis are very common. Therefore, there is ample support to the hypothesis that some and possibly most endometriosis is a physiological phenomenon.

The increasing frequency of the diagnosis

Although there is no good evidence that there is a real increase in the incidence of endometriosis in the population older clinicians report that it is a commoner diagnosis today than 30 or 40 years ago. I have already discussed that it is certainly being diagnosed with increased frequency in the infertile population. There are two possible explanations for this; either there is a real increase in the phenomenon or that we can diagnose it more easily.

If endometriosis is a disease of menstruation there is good evidence that the species is being exposed to that more frequently that ever before. In a hunter–gatherer community, as exemplified by the Kung tribe in Africa, women experience a late menarche and an early menopause, they become pregnant shortly after menarche and lactate for 3–4 years. As a result they have four to six children and are amenorrhoeic for most of their reproductive lives through pregnancy or lactation. They can expect to experience only 30 menstruations in their life. In 1994, women have the earliest menarche and latest menopause ever. In the UK, the average family size is 1.9 children and the average time for lactation is 3 months. These social changes mean that a woman can expect to be exposed to up to 450 menstruations in her reproductive life. From these data it can be concluded that the increased exposure to the event that initiates endometriosis is likely to lead to an increased prevalence of the phenomenon.

The second consideration is that the frequency of the visual diagnosis of endometriosis is really a reflection of the skill of the operator, the definition of the diagnosis and the use of biopsy. The introduction of a new diagnostic technique has created a situation where it can be postulated that a skilled surgeon
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with the best laparoscopic instruments, with enough operating time and with the ability to take as many biopsies as possible would be able to make at least a histological diagnosis of endometriosis in all premenopausal adult women. Furthermore the use of biopsy at laparoscopy has shown that ectopic endometrium can be found in many different types of lesions that would not have been considered as endometriosis previously. The denominator of the visual diagnosis has, therefore, radically changed. In conclusion two events, a change in social conditions and the introduction of a diagnostic technique, may well have combined to increase the frequency of the diagnosis without such an increase needing to be considered as a disease process.

Is endometriosis a disease?

I returned to my Oxford English Dictionary and found disease defined as: 'absence of ease..., discomfort or annoyance..., a morbid physical condition'. By definition, asymptomatic endometriosis does not fulfil a substantial part of this definition as it is not causing any discomfort to the patient. Therefore to consider it as a disease it must either be causing a problem that is important to health but does not precipitate symptoms or have the potential to become a disease as defined above i.e. it is an 'annoyance'.

The only known problem that asymptomatic endometriosis may be causing is infertility. There are abundant data that show that the diagnosis of endometriosis is commoner in infertile women compared with their fertile controls. There is no doubt that if the disease damages the tubes and ovaries it will cause infertility. However, there is no well-designed study that shows that the successful medical treatment of endometriosis improves future fertility in infertile women compared with no treatment or placebo. There are now at least five studies that have addressed this problem in a reasonably well designed manner. There can be no justification for the medical treatment of asymptomatic endometriosis in infertile women in order to improve fertility. The studies with surgical ablation of endometriosis are confusing. There are conflicting reports and the conclusions are confounded by the enormous difficulties of mounting such studies with a suitable design. In conclusion, the finding of asymptomatic endometriosis in infertile women cannot be defined as a disease.

The number of studies investigating the natural history of asymptomatic endometriosis are very small because of the logistic and ethical problems involved. Overall they report that in 30-50% of patients the endometriosis will improve or disappear over time if untreated. In the other 50% there will an increase in the amount of visible disease and in some this may include the appearance of adhesions which may themselves impact adversely upon fertility. The number of patients who became symptomatic when left untreated is very small and in at least one study no patient experienced symptoms when the disease was untreated. In none of the studies was it possible to discern prospectively in which individual the endometriosis would improve and in which
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It would deteriorate. It can be concluded, however, from the above that in some patients asymptomatic endometriosis is an ‘annoyance’ with implications to their reproductive health and therefore should be defined as a disease.

Whilst such a conclusion is valid, difficulties are encountered when recommending that asymptomatic endometriosis should be treated in order to stop it deteriorating in some women. Firstly the intervention is not without problems. Medical therapy is contraceptive and has side-effects. Its benefits should therefore outweigh its problems and such an analysis for its role in prevention of deterioration has not been performed. Furthermore ~50% of patients will be exposed to this treatment for no benefit. Surgical ablation requires the purchase of expensive equipment and has the potential for accidental damage, especially in unskilled hands and good longitudinal studies are needed to show that ablation stops deterioration of the endometriosis before it should be recommended. Probably the most negative factor for treatment as a prevention of deterioration is the fact that the disease returns. Our chairman’s own work has shown that there is a rapid return of the visual finding of endometriosis after the cessation of medical treatment. Surgical studies addressing this are few but they do show a recurrence of the disease. This leads to the inevitable problem of how often, for how long and with what do you treat an asymptomatic patient in order to prevent potential deterioration of endometriosis?. It is manifest nonsense to maintain an infertile patient on contraceptive medication to prevent deterioration of endometriosis. Equally, it is nonsensical to be repeatedly laparoscoping a woman to ablate returning or deteriorating endometriosis.

In conclusion, whilst there is no evidence that asymptomatic endometriosis is a disease in all women in that its presence alone causes infertility, in some women it could be considered a disease because it will deteriorate. However, the conflicting needs of fertility and contraceptive treatment and the impossibility of frequent surgical interventions, mean that the treatment of this phenomenon is illogical. I am delighted to see that this attitude is gaining ground among many physicians, following debates in Human Reproduction begun by Audebert et al. (1988) and Koninckx (1994), with later contributions from several workers (Brosens, 1994; Evers, 1994; Berqvist, 1995; Moen, 1995).

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I conclude that a proportion, if not the majority, of the visual diagnoses of asymptomatic endometriosis are describing a physiological phenomenon that can be explained biologically and by changes in social conditions and diagnostic techniques. The lack of a clear causal relationship with infertility and the impossibility of providing a rational basis for treatment means that there is no imperative to treat the phenomenon. Therefore I can only logically conclude the asymptomatic endometriosis has no relevance to reproductive medicine or surgery at present. In fact, attribution of abnormality to the phenomenon may be harmful. If we accept that small amounts of endometriosis are common and irrelevant it
is inevitable that they will be found in women with pelvic pain in whom they are coincidental. Causality will, however, be attributed and these patients are then labelled as having endometriosis and subjected to a number of treatments which are valueless. I find that more and more of my tertiary referral clinic is involved in extricating patients from the diagnosis of endometriosis rather than verifying it.

Perhaps the best way to view asymptomatic endometriosis is that it is no more than a marker for potential problems. It does not require treatment but it does require a strategy for monitoring. The exact nature of this strategy will depend upon the patient. At one end of the spectrum the woman with a small amount of asymptomatic disease found at laparoscopic sterilisation will require no monitoring at all and there could be considerable debate as to whether she should be informed of the finding. We would not normally consider it necessary to inform patients of physiological findings observed during medical investigations. At the other end of the spectrum will be the infertile woman under intense investigation in whom the presence of asymptomatic endometriosis may initiate an earlier referral for advanced reproductive treatment because it is known that the phenomenon may deteriorate and adversely affect her reproductive health. The important factor is that the clinician thinks about the relevance of the finding to that particular patient with her particular problems, at that particular time of her life and in the light of her therapeutic ambitions. Once all those factors are considered, a sensible strategy can be designed.

**The acceptance of asymptomatic endometriosis as physiological**

I am aware that much of what I have written above will be unacceptable to many clinicians. However I am not alone and the only reference I will use is that which was a consensus statement of a number of European gynaecologists which echoes many of the concepts I have introduced (Audebert et al., 1988). It is fascinating and educational to speculate on why many clinicians are unwilling to accept that asymptomatic endometriosis may be normal and it give insights into our understanding of disease.

We have always considered endometriosis to be a disease historically and many of us were trained in that environment. It is understandable that we are reluctant to let go of the concepts that respected teachers gave us. The finding often occurs as something positive in patients in whom no other diagnosis has been made. Examples of this are in infertility and in complex pelvic pain. It is natural that the clinician will be relieved to have found a potential explanation and inevitable that they will use that in their discussions with the patient. Understandably, the patient is going to be pleased that an explanation has been found and will collude with the establishment of this phenomenon as a disease model. Perhaps the best example of this is the reaction of some doctors and patients to the papers reporting microscopic endometriosis. Few of us would argue that visually normal peritoneum in an asymptomatic patient should be
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regarded as normal. The fact that it may contain microscopic amounts of a physiological tissue would not alter that perception. However, I am frequently approached by both clinicians and patients arguing that it represents a disease and thus normal peritoneum should be excised. The final absurdity here is to conclude that all women have a complete excision of their peritoneal mesothelium because it is highly likely that microscopic endometriosis is ubiquitous in the pre-menopausal adult human female.

The other main factor which affects our perception is the momentum for treatment precipitated by drugs and surgery. Pharmaceutical companies can only be guided by expert gynaecologists who have informed them for a number of years that endometriosis is a disease. Both they and those self-same experts are going to be resistant to accepting that in many cases this is not the case not only because of the loss of sales but also because of the admission of error. I am not implying that any of these actions are ever explicitly taken but they will subliminally affect both the company’s and the expert’s approach to the problem. For the record I am one of those experts myself so I am aware of the pressures such an admission cause me. The same concepts apply in surgery. It is very difficult to have purchased large amounts of expensive equipment and undergone a long training to learn to treat endometriosis and then to admit that most of the time it is unnecessary. For some individuals their livelihood depends upon this and I cannot think of a more effective intellectual block than financial hardship. Again I am not inferring that any of this works explicitly but it will have a subliminal influence.

I hope that above comments have stimulated thought into how a phenomenon enters a disease model and the main purpose for bringing them to your attention is to provide a structure around which all clinicians can analyse their decision to treat a patient. I think the final statement should be left to an unidentified Edinburgh physician who is reputed to have said: 'It is a very, very clever doctor who can make an asymptomatic patient feel better'.

References