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DEBATE

'Waiting for Godot'†: a commonsense approach to the medical treatment of endometriosis

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ABSTRACT: Conservative surgical treatment for symptomatic endometriosis is frequently associated with only partial relief of pelvic pain or its recurrence. Therefore, medical therapy constitutes an important alternative or complement to surgery. However, no available compound is cytoreductive, and suppression instead of elimination of implants is the only realistic objective of pharmacological intervention. Because this implies prolonged periods of treatments, only medications with a favourable safety/tolerability/efficacy/cost profile should be chosen. In the past few years, innumerable new drugs for endometriosis, which would interfere with several hypothesized pathogenic mechanisms, have been studied and their use foreseen. However, robust evidence of *in vivo* safety and efficacy is lacking and, at the moment, the principal modality to interfere with endometriosis metabolism is still hormonal manipulation. Regrettably, in spite of consistent demonstration of a major effect on pain even in patients with deeply infiltrating lesions, progestins are underestimated and dismissed in favour of more scientifically fashionable and up-to-the-minute alternatives. Moreover, oral contraceptives (OCs) dramatically reduce the rate of post-operative endometrioma recurrence and should now be considered an essential part of long-term therapeutic strategies in order to limit further damage to future fertility. Finally, women who have used OC for prolonged periods will be protected from an increased risk of endometriosis-associated ovarian cancer. To avoid the several subtle modalities for distorting facts and orientating opinions in favour of specific compounds, progestins and monophasic OC used continuously are here proposed as the reference comparator in all future randomized controlled trials on medical treatment for endometriosis.

Key words: endometriosis / pelvic pain / medical treatment / oral contraceptives / progestins

Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disease (Giudice, 2010) that can be effectively cured by definitive surgery (Shakiba *et al.*, 2008), an option generally not accepted by patients wishing to preserve fertility. Because conservative surgery is often associated with only partial relief or recurrence of symptoms (Vercellini *et al.*, 2009a,b), prolonged medical therapies may be needed for endometriosis, as for most chronic inflammatory disorders in general. Also according to the Practice Committee of the American Society for Reproductive Medicine (2008), 'endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures'.

Women with endometriosis tend to undergo a great deal of suffering, and the symptoms they can experience may be caused by both insufficient control of inflammation and side effects of drugs (Vercellini *et al.*, 2008a, 2009c; Allen *et al.*, 2009). Researchers are looking for new ways to treat such a condition, and many women may be eligible for clinical trials in which various therapeutic approaches are tested. Participating in such trials can benefit patients as individuals and science as a whole by contributing useful generalizable information. However, it has been reported recently that although several clinical trials evaluating the efficacy of various new compounds for endometriosis are listed as completed at ClinicalTrials.gov, the results of only a few have been published (Guo *et al.*, 2009). Almost all of the completed clinical trials for which no information on their outcome is available in the public domain were sponsored by pharmaceutical companies.

The reason for not reporting data is presumably related to problems in efficacy, safety or both and, on this basis, it has been inferred that evidently no optimal drug for endometriosis yet exists. Moreover, possibly because of the unexpectedly high risk/benefit ratios

†By Samuel Beckett, 1952.

uncovered in the above trials, greater difficulties than originally realized are foreseen in the development of novel and efficacious therapeutics to treat endometriosis-associated symptoms (Guo *et al.*, 2009).

In the past few years, many experts published reviews on forthcoming medications for the disease (D'Hooghe, 2003; Nothnick and D'Hooghe, 2003; Fedele and Berlanda, 2004; Olive *et al.*, 2004; Attar and Bulun, 2006; Chlouber *et al.*, 2006; Crosignani *et al.*, 2006a; Mihalyi *et al.*, 2006; Hompes and Mijatovic, 2007; Fedele *et al.*, 2008; Guo, 2008; Panay, 2008; Ferrero *et al.*, 2010a) and concluded that we were entering a new therapeutic era when several compounds would become available which could act on aetiological mechanisms, thereby radically changing the management and prognosis of endometriosis. Regrettably, the situation appears considerably different.

An alternative to not reporting at all trial results is publication of selected data only (biased reporting). Rising *et al.* (2008) demonstrated a major gap between information submitted to the Food and Drug Administration regarding new drug applications during the period 2001–2002, and information eventually reaching medical journals. Trials with favourable outcomes were nearly five times as likely to be published as those with unfavourable outcomes, and a relevant amount of data on primary outcomes has not been reported. Finally, discrepancies have been observed between type of outcomes, statistical analyses and conclusions presented in new drug applications and those appearing in journal articles. The majority of these discrepancies were in favour of the new drug. This is particularly worrying as publication of reports in 'peer-reviewed' journals constitutes the most important source of information on novel drugs for physicians who generally have limited clinical experience with the latest treatments. In addition, there are also substantial economic implications if efficacy is overestimated and the medication over-utilized, given that usually new molecules are among the most costly drugs on the market.

In light of this scenario, we deem it important to define the fundamental principles that should guide medical treatment for endometriosis, reconsidering the pathogenic basis on which novel drugs for the disease could be developed and the methodological issues that should be addressed in future research in this field.

The unpalatable taste of medical therapies

Medical treatment should ideally eradicate endometriosis rather than merely relieving its symptoms (Fedele and Berlanda, 2004). However, in case a cytoreductive compound would be developed, which can effectively eliminate endometriotic lesions, it is difficult to comprehend how this effect would be limited to ectopic but not eutopic endometrium. In fact, endometriosis appears to originate from intrauterine endometrium, and the receptor pattern and the biologic behaviour of the two mucosae are substantially similar (Noel *et al.*, 2010). Therefore, pharmacological destruction of pelvic implants, if at all possible, would carry a high risk of damage to normally located mucosa, with potential consequences on menstrual pattern, fertility, and future pregnancies. As a compound with selective properties only against the ectopic endometrial cell has not yet been synthesized, for the present the therapeutic target is not endometriosis cytoreduction, but suppression, which implies the survival of ectopic implants independently of the drug type, dosage, and duration of use (Evers, 1987). Consequently, if medical treatment is indicated, it might be required for years, or until the patient seeks conception.

If the notion of 'control' instead of 'cure' of endometriosis is accepted, then caution should be paid to the overall therapeutic profile of any 'old' or 'new' medication prescribed in clinical practice or assessed within a research setting. Indeed, efficacy in terms of symptoms' relief is just one of the outcomes to be considered, especially in long-term therapies. Numerous clinical studies and systematic reviews have consistently demonstrated that hormonal compounds with very dissimilar pharmacological profiles determine comparable pelvic pain reduction. This is acknowledged in several guidelines on the treatment of endometriosis (American College of Obstetricians and Gynecologysts, 2000; Kennedy *et al.*, 2005; Royal College of Obstetricians and Gynaecologysts, 2006; Practice Committee of the American Society for Reproductive Medicine, 2008; Society of Obstetricians and Gynaecologysts of Canada, 2010). Therefore, pain relief *per se* may not be the main factor for the choice of the drug to be used. Disease control may result in an acceptable improvement of quality of life, only if also safety, tolerability and costs of medications are taken into adequate account. In addition, more weight must be given to patients' views of treatments and to the outcome they consider to be the most important. In fact, it has been properly considered that 'patient oriented outcomes [. . .] make a difference to the daily lives of women with endometriosis' (Farquhar, 2000).

The general principles that should guide medical management of endometriosis are not different from those applicable to other chronic inflammatory disorders: achievement of long phases of disease remission is the reasonable goal, and reappearance of symptoms at drug discontinuation must not be considered as a demonstration of inefficacy of therapy.

The wonder drugs: hope or hype?

Innumerable pharmacological treatments for endometriosis have been proposed based on many hypothesized pathogenic mechanisms or supposedly selective hormonal responsiveness. Interference with implantation, neo-angiogenesis, proliferation, atypical metabolism, abnormal immunologic reactions, inflammation and apoptotic activity have been tried. A tentative list of these compounds is reported in Table I. To understand the different characteristics of these drugs and the main results observed in the various studies, reference is made to the many comprehensive reviews published on the topic (D'Hooghe, 2003; Nothnick and D'Hooghe, 2003; Fedele and Berlanda, 2004; Olive *et al.*, 2004; Attar and Bulun, 2006; Chlouber *et al.*, 2006; Crosignani *et al.*, 2006a; Mihalyi *et al.*, 2006; Hompes and Mijatovic, 2007; Fedele *et al.*, 2008; Guo, 2008; Panay 2008; Ferrero *et al.*, 2010a). Several experts maintain that the development of non-hormonal medical treatments to prevent or treat endometriosis and associated symptoms is a priority and that such treatments should reduce pain and subfertility without suppression of ovulation, providing the option of a normal and safe pregnancy during treatment. They also recommend evaluating drugs that interfere with inflammation [tumour necrosis factor (TNF)-α inhibitors; cyclooxygenase (COX)-2 inhibitors], fibrosis and angiogenesis, and matrix metalloproteinases (Rogers *et al.*, 2009).

However, the solution is not yet at hand, and several of the compounds included in Table I are associated with uncertain or no efficacy, such as pentoxifylline (Lv *et al.*, 2009) or anti-TNF-α (Lv *et al.*, 2010)

Table I Experimental drugs and proposed future therapeutic schemes for endometriosis (literature data 1987–2010).

Anti-angiogenetic agents
Cabergoline
Endostatin
Sirolimus
Thalidomide
Vascular endothelial growth factor inhibitors
Antioxidants
N-acetylcysteine
Vitamin E succinate
Aromatase inhibitors
Anastrozole
Fadrozole
Formestane
Exemestane
Letrozole
Anastrozole plus oral contraceptive
Anastrozole plus GnRH analogue
Anastrozole plus progesterone, calcitriol and rofecoxib
Letrozole plus norethindrone acetate, calcium citrate and vitamin D
COX-2 inhibitor
Celecoxib
Indomethacin
Nimesulide
Rofecoxib
Valdecoxib
GnRH antagonists
Abarelix
Cetrorelix
Histone deacetylase inhibitors
Trichostatin A
Valproic acid
Valproic acid plus retinoic acid
Immunomodulators
Acetylcholine nicotine receptor analogue—Levamisole
Cytokines interleukin -12
Guanosine analogue—Loxoribine
Interferon-$\alpha_{2\beta}$
Rapamycin
Xantine analogue—Pentoxifylline
Mitogen-activated protein kinase inhibitors
FR167653
p38 inhibitor
Matrix metalloproteinases inhibitors
ONO-4817
Nuclear factor kappa B inhibitors
Caffeic acid phenethyl ester
Capsaicin
SN-50
Perossisome proliferator-activated receptor-γ (Thiazolidinediones)
Rosiglitazone
Troglitazone
Progesterone antagonists
Mifepristone (RU 486)
Onapristone
Selective PR modulators
Asoprisnil
J-956 (asoprisnil ecamate)
J-1042 (megestrone)
Selective estrogen receptor β agonists
ERB-041
Selective estrogen receptor modulators
Fulvestrant
Raloxifene
Tamoxifen
Statins
Atorvastatin
Lovostatin
TNF blockers
Chimeric anti-TNF-α monoclonal immunoglobulin—Infliximab
TNF-α receptor-immunoglobulin fusion protein—Etanercept

Data from Fedele and Berlanda (2004), Olive *et al.* (2004), Attar and Bulun (2006), Chlouber *et al.* (2006), Fedele *et al.* (2008), Guo (2008), Panay (2008), Vercellini *et al.* (2009c) and Ferrero *et al.* (2010a).

and, most importantly, with potentially severe side effects. Some of the study drugs have been investigated in oncology as experimental therapies in patients without alternative options (e.g. immunomodulators, anti-TNF-α, anti-angiogenetic compounds), and little is known of safety after prolonged use. The risk of major untoward effects may be acceptable in the above clinical context, but not in otherwise healthy women affected by a benign condition. Even when off-label use of routinely prescribed drugs, such as COX-2 inhibitors, statins and valproic acid, is envisaged, the balance between potential benefits and demonstrated risks should be carefully elaborated. At present, it appears that the principal modality to effectively achieve adequate lesion suppression and interfere with endometriosis progression is still hormonal manipulation.

Challenging conventional biologic wisdom

The efficacy of endometriotic lesion suppression with progestins has been recently questioned based on a purported progesterone resistance in both eutopic and ectopic endometrium of women with the disease. This would explain why ~9% of patients do not respond to progestin treatment (Guo, 2009).

The expression of human progesterone receptor (PR) is controlled by two promoters that direct the synthesis of mRNA transcripts encoding two receptor proteins, PR-A and PR-B. The different transcriptional activities of the two isoforms, and the inhibitory activity of PR-A on PR-B *in vitro*, suggest that tissues that express different relative levels of the two proteins, and in particular, high levels of PR-A, may have impaired responsiveness to progesterone and other nuclear receptor ligands. In breast and endometrial cancers, such alterations in the PR-A/PR-B ratio induced a marked effect on cell morphology, a consistent loss of adherent properties and features of invasive behaviour (McGowan *et al*., 2003).

Independent investigators suggested that an alteration of the relative expression of PR-A and PR-B in endometrial cells may play a pivotal role also in the pathogenesis of endometriosis, leading to impaired stromal differentiation and a consequent relative resistance to progesterone action. A decreased PR-B/PR-A ratio has been demonstrated not only in ectopic tissue (Attia *et al*., 2000), but also in eutopic endometrium of women with endometriosis (Igarashi *et al*., 2005), albeit not consistently (Bukulmez *et al*., 2008). The down-regulation of PR-B expression as a consequence of the hypermethylation of the gene promoter region has also been observed by Wu *et al*. (2006) in epithelial cells of some ectopic foci.

However, within the context of basic research on endometriosis, it is often difficult to distinguish between a primary aetiologic factor and alterations occurring with time or under peculiar hormonal and inflammatory conditions at both transcriptional and non-transcriptional levels. The inflammatory environment constitutes, in itself, a trigger for epigenetic reprogramming, e.g. through local extracellular acidosis and deposit of reactive substances. Reactive halogen compounds, which are a by-product of many chemical reactions produced by inflammatory processes, cause DNA methylation alteration. Chemical transformations of DNA methylation contributes to disruption of the epigenetic code, which could result in a disturbed readout by the methylation-binding proteins involved in both activating and silencing of genes (Bäckdahl *et al*., 2009). Therefore, it cannot be excluded that secondary events, such as the increased inflammatory response observed in ectopic endometrium, may contribute to the differential receptor expression pattern demonstrated in some endometriotic lesions. Of note, the induction of experimental disease in mice leads to a completely opposite hormonal receptor expression, as total endometrial PR and PR-B were shown to be increased, and PR-A decreased in animals with endometriosis, thereby supporting not only the idea that alterations are secondary to disease establishment, but also that PR levels are highly susceptible to local and variable conditions (Lee *et al*., 2009).

More information is definitely needed on why, when and to what extent, progesterone response is disrupted in women with endometriosis. Given the complexity of the endometrial and endocrine systems, great caution should be maintained before inferring clinical considerations based on observational basic research findings, especially in the case of a disease that involves different cell populations, different biological systems and a great number of cellular functions.

Pharmacological extravagance

In the past few years, aromatase inhibitors have been acclaimed as the next generation of therapeutics (D'Hooghe, 2003; Attar and Bulun, 2006; Patwardhan *et al*., 2008; Bulun, 2009), but a careful approach is needed with these drugs used as chemopreventive agents after surgery for breast cancer (American College of Obstetricians and Gynecologysts, 2008).

The aromatase enzyme is expressed in several tissues (including breast, ovary, endometrium, placenta, testes, skin, bone, fat and brain) where it mediates the *in situ* conversion of androstenedione to oestrone and of testosterone to estradiol. It has been suggested that aromatase is expressed at higher levels in endometriosis implants than in normal endometrium, thus providing the ectopic mucosa with excessive proliferative stimulus (Attar and Bulun, 2006; Bulun, 2009). This finding has prompted performance of several pilot studies in women with endometriosis using one of the two available reversible aromatase inhibitors (i.e. anastrozole and letrozole), which compete with androgens for aromatase-binding sites (Patwardhan *et al*., 2008; Ferrero *et al*., 2009a). Irreversible inactivators, such as exemestane, are contraindicated in patients desiring future conception. However, again it is unclear if the increased expression of this cytochrome P-450 complex constitutes the very reason for survival and proliferation of regurgitated endometrial cells, or if it is the consequence of local inflammation, as it has been demonstrated that prostaglandins are among the most potent inducers of aromatase activity in endometriotic cells (Noble *et al*., 1997), in which case, aromatase inhibitors would simply treat an epiphenomenon.

Moreover, during the reproductive period, aromatase inhibitors stimulate ovarian function, as they reduce the hypothalamic-pituitary estrogen feedback, with consequent rise in GnRH secretion, elevations in FSH and LH, and augmented follicular development. Indeed, aromatase inhibitors have been suggested to correct ovulatory dysfunction as well as to increase the number of follicles in controlled ovarian stimulation protocols (Casper, 2009). Therefore, in premenopausal women, these compounds must be used together with other drugs [e.g. GnRH agonists, danazol, oral contraceptives (OCs), progestins] that could effectively suppress gonadotrophins and reduce ovarian activity (Soysal *et al*., 2004; Ailawadi *et al*., 2005; Amsterdam *et al*., 2005). Clearly, when these combined regimens are used for endometriosis, it is impossible to assess how much of the effect on pain is related to which of the two medications (Remorgida *et al*., 2007a).

When the efficacy of letrozole plus norethisterone acetate (NETA) was compared with that of NETA alone in women with rectovaginal endometriosis (Ferrero *et al*., 2009b), the reported intensity of pelvic pain was slightly lower in the combined regimen group but, owing to the side effects of letrozole (mainly joint pain and myalgia), satisfaction with treatment was higher in subjects who used NETA alone. After treatment discontinuation, symptoms recurred without significant between-group differences, demonstrating that also aromatase inhibitors are neither cytoreductive nor curative. In fact, histological examination of endometriotic lesions excised after treatment with letrozole shows preservation of endometrial glands and high stromal proliferative activity (Remorgida *et al*., 2007a). Thus, also treatments with these combined regimens should be prolonged if disease suppression is to be maintained, but this would generate problems of safety (e.g. potential reduction in bone mineral density), cause additional untoward effects and increase costs.

Aromatase inhibitors seems effective in treating severe postmenopausal endometriosis through blockade of extraovarian estrogen

production (American College of Obstetricians and Gynecologists, 2008), but their use in premenopausal endometriosis should be considered with caution (Ferrero *et al*., 2009a). The aim of pursuing the deepest possible hypo-estrogenism even within ectopic implants is not supported by demonstration of lower probability of lesion and symptoms reappearance at drug withdrawal (Remorgida *et al*., 2007a,b; Ferrero *et al*., 2009b). Finally, the implication of ectopic aromatase production in the development of endometriosis has recently been questioned and should be further elucidated (Colette *et al*., 2009; Colette and Donnez, 2009; Delvoux *et al*., 2009).

Life is now!

Better drugs for endometriosis hopefully will be available in the future, but patients suffering today desperately demand therapeutic answers now. The only current, meaningful modality to substantially alleviate pain is suppression of ovarian function and induction of a steady hormonal condition, anovulation and, eventually, amenorrhoea. The steroidal environment should be modulated to avoid excessive hypo-estrogenism as well as hyper-androgenism. In both cases, subjective and metabolic untoward effects would considerably undermine safety and tolerability.

Such hormonal modifications could be maintained from diagnosis to conception seeking, or as an alternative to surgery after completion of family. In fact, prescribing medications for a few months has no clear rationale and exposes women to extenuating recurrences of symptoms and lesions and to the risk of repetitive surgery. Accordingly, given the potential duration of treatment, a careful balance should be made between benefits, risks and costs of the drugs used. Progestins and OCs allow a practical combination of these aspects (Vercellini *et al*., 1997, 2003a; Davis *et al*., 2007).

A MEDLINE search conducted from January 1990 to July 2010 through the English language literature (MeSH terms: endometriosis, progestins, OCs, medical therapy), identified nine controlled trials in which a progestin or an OC was compared with an alternative hormonal compound to treat symptomatic endometriosis. Details are shown in Table II. Study quality was not assessed. The results consistently confirmed that progestins and OCs are effective in relieving pain, generally well-tolerated, and not inferior to danazol, GnRH agonists and aromatase inhibitors (Vercellini *et al*., 1993, 1996; Prentice *et al*., 2000, 2004; Cosson *et al*., 2002; Petta *et al*., 2005; Schlaff *et al*., 2006; Crosignani *et al*., 2006b; Davis *et al*., 2007; Selak *et al*., 2007; Harada *et al*., 2009; Ferrero *et al*., 2009b; Strowitzki *et al*., 2010a).

OC, used cyclically or continuously, may constitute an adequate first-line option for peritoneal and ovarian endometriosis (Vercellini *et al*., 2003b, 2008a, 2009c), whereas low-dose oral NETA is probably the best choice for rectovaginal lesions (Vercellini *et al*., 2005, 2009d; Remorgida *et al*., 2007a; Ferrero *et al*., 2009b, 2010b,c). The extensive epidemiologic information available demonstrates that OCs and progestins are the safest medical alternative for long-term treatments of endometriosis (American College of Obstetricians and Gynecologysts, 2010; Cibula *et al*., 2010; Hannaford *et al*., 2010). Finally, women who have used OC for prolonged periods might be reassured that they will be protected from an increase in risk of endometriosis-associated ovarian cancer (Missmer *et al*., 2004).

Prevention of recurrence? Yes we can!

Endometriosis has a distinctive tendency to recur after conservative surgery (Shakiba *et al*., 2008; Guo, 2009). The persistence of pathogenic mechanisms and the recent trend towards delaying pregnancy result in a considerable rate of post-operative disease and symptoms relapse, which gradually increases throughout the years (Vercellini *et al*., 2009e, 2010). According to Evers *et al*. (1991), 10% of patients redeveloped signs and symptoms of endometriosis after a 1-year follow-up period, 25% after 3 years and 45% after 5 years. Also DeCherney (1992) maintains that the endometriosis annual recurrence rate may be as high as 15% and that cumulative rates ~40% after 3–5 years. Recently, Guo (2009) calculated that the disease relapse rate is higher than 20% at 2 years and 40–50% at 5 years. In particular, data are accumulating on the post-operative endometrioma recurrence rates, which reportedly vary between 30 and 50% after 2–5-year follow-up (Kikuchi *et al*., 2006; Koga *et al*., 2006; Vercellini *et al*., 2008b).

The consequences of endometriosis relapse on reproductive performance may be particularly detrimental, owing to peritoneal as well as gonadal damage caused by both recurrent disease and repeated surgical trauma (Vercellini *et al*., 2009e). Moreover, pain symptoms relapse exposes patients to repetitive suffering, frustration, multiple courses of medical therapy and risk of serial surgery. Therefore, the possibility of preventing recurrences after conservative surgery is essential to achieve an acceptable quality of life and to preserve the already reduced reproductive potential (Rogers *et al*., 2009).

Several lines of evidence support the role of OCs in the tertiary prevention of endometriomas. In fact, ovulation seems crucial in the development of ovarian endometriotic cysts (Jain and Dalton, 1999; Vercellini *et al*., 2009f), and its suppression should substantially decrease the likelihood of cyst reappearance after laparoscopic treatment. Numerous uncontrolled studies indicate that post-operative OC exposure is associated with a major reduction in the risk of endometrioma recurrence (Seracchioli *et al*., 2009; Vercellini *et al*., 2010). A MEDLINE search conducted from January 2000 to July 2010 through the English language literature (MeSH terms: endometriosis, endometrioma, recurrence, OC, laparoscopy), identified three controlled studies (Table III) reporting the incidence of post-operative endometrioma recurrence in long-term (≥2 years) OC users compared with non-users (Vercellini *et al*., 2008b; Takamura *et al*., 2009; Seracchioli *et al*., 2010a). Studies reporting the short-term (6 months) post-operative OC use were not considered (Muzi *et al*., 2000; Yap *et al*., 2004; Sesti *et al*., 2007). A dramatic reduction in the risk of reappearance of endometriotic cysts in OC users was consistently observed independent of cyclic or continuous use, with odds ratios varying from 0.04 (Takamura *et al*., 2009) to 0.32 (Seracchioli *et al*., 2010a). Moreover, the results of two randomized controlled trials (RCTs; Vercellini *et al*., 2003c; Abou-Setta *et al*., 2006; Seracchioli *et al*., 2010b; Table IV) demonstrated the efficacy of prolonged progestins and OC use also in the prevention of post-operative symptoms recurrence. Thus, the solution to avoid repetitive short-term medical treatments and multiple laparoscopies appears already at hand (Seracchioli *et al*., 2009), and women not seeking

Table II Effect of OCs and progestins as assessed in controlled trials on the treatment of symptomatic endometriosis (literature data, 1990–2010).

Source	Study design	Number of patients enrolled	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Vercellini *et al.* (1993)	RCT open	57	EE 0.02 mg + DSG 0.15 mg/day per os ($n = 28$)	Goserelin 3.6 mg depot s.c. injections/ 28 days ($n = 29$)	6 months	6 months	Significant reduction in dysm and CPP; goserelin better for dysp; similar pain at follow-up
Vercellini *et al.* (1996)	RCT open	80	DMPA 150 mg i.m. injections/3 months ($n = 40$)	Danazol 50 mg/day per os + low-dose monophasic OC ($n = 40$)	12 months	No follow-up	Similar pain relief and degree of satisfaction
Cosson *et al.* (2002)	RCT multicentre open	142	Dienogest 2 mg/day per os ($n = 74$)	Triptorelin 3.75 mg depot i.m. injections/ 28 days ($n = 68$)	4 months	12 months (reproductive outcome only)	Similar pain relief after LPS; no pain evaluation at follow-up
Petta *et al.* (2005)	RCT multicentre open	82	LNG-IUD ($n = 39$)	Leuprolide 3.75 mg depot i.m. injections/ 28 days ($n = 43$)	6 months	No follow-up pain evaluation	Similar pain relief and psychological well-being. More bleeding with IUD
Crosignani *et al.* (2006b)	RCT multicentre evaluator-blinded	299	DMPA 104 mg s.c. injections/3 months ($n = 153$)	Leuprolide 3.75 or 11.25 mg depot s.c. or i.m. injections/ 28–90 days ($n = 146$)	6 months	12 months	Similar pain relief and improvement in QoL and productivity. Less BMD decline with DMPA
Schlaff *et al.* (2006)	RCT multicentre evaluator-blinded	274	DMPA 104 mg s.c. injections/3 months ($n = 136$)	Leuprolide 11.25 mg depot i.m. injection/3 months ($n = 138$)	6 months	12 months	Similar pain relief and improvement in QoL and productivity. More bleeding but less hypo-estrogenic side effects and BMD loss with DMPA
Harada *et al.* (2009)	RCT double-dummy	271	Dienogest 2 mg/day per os ($n = 137$)	Buserelin 900 mg/day IN ($n = 134$)	6 months	No follow-up	Similar pain relief and improvement in QoL. More bleeding, but less hypo-estrogenic side effects and BMD loss with dienogest
Ferrero *et al.* (2009a,b)	PPT	82	Letrozole 2.5 mg + NETA 2.5 mg/day per os ($n = 41$)	NETA 2.5 mg/day per os ($n = 41$)	6 months	12 months	Greater pain relief with letrozole + NETA, but fewer side effects and higher patients' satisfaction with NETA only. Similar pain at follow-up
Strowitzki *et al.* (2010a)	RCT multicentre open	252	Dienogest 2 mg/day per os ($n = 124$)	Leuprolide 3.75 mg Depot IM injections/ 28 days ($n = 128$)	6 months	No follow-up	Similar pain relief. Higher improvement in QoL with dienogest. More bleeding but less hypo-estrogenic side effects and BMD loss with dienogest

EE, ethinyl-estradiol; DSG, desogestrel; Dysm, dysmenorrhoea; Dysp, dyspareunia; CPP, noncyclic chronic pelvic pain; DMPA, depot medroxyprogesterone acetate; OC, oral contraceptive; LPS laparoscopy; LNG-IUD, levonorgestrel-releasing intrauterine device; QoL, quality of life; BMD, bone mineral density; IN, intranasally; PPT, patient preference trial; NETA, norethisterone acetate.

immediate conception must systematically receive detailed information in this regard.

Scientific glasnost

Scientific facts may be distorted and opinions manipulated not only by limiting publication of clinical-trial results (Rising *et al.*, 2008; Guo *et al.*, 2009), but also through other, probably more subtle and potentially even more dangerous, modalities (Chan, 2008). One of the methods to sway the evidence could be selecting the outcome in relation to the 'experimental' compound being investigated (Lee *et al.*, 2008). For example, if a pharmaceutical company is interested in emphasizing the superiority of a GnRH agonist over danazol, the effect on lipid profile might be chosen as the main outcome of the

Table III Results of studies comparing the endometrioma recurrence rate in women undergoing laparoscopic excision of ovarian cysts followed by a long-term post-operative oc use versus em (literature data, 2000–2010).

Source	Study design	Patients enrolled (*n*)	Follow-up (months)	Number of recurrence in OC group (%)	Number of recurrence in EM group (%)	OR	95% CI
Vercellini *et al.* (2008b)	Cohort	277	28	9/102[a] (9)	26/46 (56)	0.07	0.03–0.18
Takamura *et al.* (2009)	Cohort	87	24	1/34[a] (3)	17/39 (44)	0.04	0.00–0.32
Seracchioli *et al.* (2010a)	RCT	239	24	17/148[b] (11)	20/69 (29)	0.32	0.15–0.66

EM, expectant management; OR, odds ratio; CI, confidence interval.
[a]Only 'always OC users' are considered.
[b]Cyclic and continuous OC users are considered together.

Table IV Results of RCTs comparing the dysmenorrhoea recurrence rate in women undergoing laparoscopic treatment of endometriosis followed by post-operative progestin or oc use versus expectant management (literature data, 2000–2010).

Source	Patients enrolled (*n*)	Post-operative intervention	Follow-up (months)	DYSM recurrence in progestin/OC group [*n* (%)]	DYSM recurrence in EM group [*n* (%)]	OR	95% CI
Vercellini *et al.* (2003c)	40	LNG-IUD	12	2/20 (10)	9/20 (45)	0.14	0.02–0.75
Seracchioli *et al.* (2010b)	311	Continuous/cyclic OC	18	33/187[a,b] (18)	35/87 (40)	0.32	0.18–0.56

[a]Cyclic and continuous OC users are considered together.
[b]Only subjects who completed the study are considered.

study. Conversely, if the superiority of danazol or of a similar medication (e.g. gestrinone) is to be demonstrated, the main outcome could well be the effect on bone metabolism. Alternatively, if the antalgic properties of a drug are to be shown, what better than a placebo-controlled study, given that the placebo-effect is short-lived in this clinical condition (Fedele *et al.*, 1989). This would appear as an elegant study design, which at the same time would not be exposed to the risk of unfavourable evaluations with active comparators. However, six RCTs have already demonstrated that various treatments used for the relief of pain in women with symptomatic endometriosis are far superior to placebo (Telimaa *et al.*, 1987; Dlugi *et al.*, 1990; Fedele *et al.*, 1993; Bergqvist *et al.*, 1998; Harada *et al.*, 2008; Strowitzki *et al.*, 2010b).

To prevent the above risks, we propose monophasic OCs taken continuously or low-dose NETA as the reference comparators in all future RCTs on medical treatments for endometriosis. Moreover, we wonder if pain relief should be considered as the most appropriate main outcome. Given the similarity in effect size of the available drugs, how many hundreds of patients would need to be recruited to identify a statistically significant difference? And even when such a difference is detected, would it still be clinically important? In our opinion, satisfaction with treatment, a simple and clear measure that allows little margin for manipulation, should be chosen as the outcome that offers the most realistic view of the overall impact of any given compound on health-related quality of life.

Furthermore, given that medical therapies for endometriosis are not curative, are classic 6-month trials still justified? In our view, studies lasting less than 1 year should not be planned, in order to offer a reliable impression of the tolerability of the compounds being evaluated. Indeed, when patients know that they will have to use a drug for only a few months, they are probably more prone to tolerate its' side effects and avoid withdrawal. However, this would be less likely if they knew that the treatment period would be longer.

Finally, only intention-to-treat analyses, including all recruited subjects, should be considered appropriate. Taking into account only efficacy analyses, and excluding dropouts with the justification that complete pain diaries are not available, usually determines an overestimate of treatment efficacy and tolerability. In fact, dropouts are usually largely dissatisfied because of persisting pain or development of major side effects. If the number of dropouts is substantially different between two treatment arms, their exclusion may easily result in a spurious demonstration of equivalence of effect size or 'non-inferiority'.

'Money for nothing' (Dire Straits, Vertigo, UK, 1985)

Information on the cost of endometriosis to patients and society is limited. According to studies based on 2002 US data, the global cost of the disease (including analgesics, hormonal therapies, gynaecological consultations, hospital admissions, surgical procedures, days off-work and reduced productivity) varies between $18.8 and $22 billion per year (Gao *et al.*, 2006; Simoens *et al.*, 2007), which is substantially higher than the estimated costs of other chronic disorders, such as Crohn's disease ($865 million) and migraine ($13–17 billion; Rogers *et al.*, 2009).

Also the therapeutic approach selected may influence the expenses for disease management. As an example, implementation of a tertiary prevention strategy with OCs or progestins after surgery is associated with a decrease in symptoms and lesions recurrence (Vercellini *et al*., 2008b, 2010; Seracchioli *et al*., 2009, 2010a,b; Takamura *et al*., 2009), with a potential major impact on the above cost indicators. Other pharmacological compounds do not seem to guarantee better long-term results and are much more expensive. There are huge differences in the annual cost of therapy depending on the type of medication chosen, ranging from €18 for low-dose NETA to around €2100 for aromatase inhibitors or GnRH agonists (Vercellini *et al*., 2009d). Some authors even suggest combining the latter two drug categories (Soysal *et al*., 2004; Guo, 2008), with a yearly expenditure of about €4200.

In a world with decreasing health resources, decision-makers should establish their decisions based on a patient-centred view built on the most up-to-date available evidence (Al-Inany, 2008). Public health institutions should take into account the recommendations of major gynaecologic associations, and reimburse expensive therapies for endometriosis only in limited circumstances (e.g. when OCs and progestins have failed or when they are contraindicated or not tolerated). 'Disease mongering' has been defined as the selling of sickness that widens the boundaries of illness and increases the market for those who sell and deliver treatments (Moynihan and Henry, 2006). In this context, 'drugs are prescribed by physicians to people for whom use of the drug has been deemed not cost-effective because of a poor cost-benefit ratio. Public money is wasted [...] in part as a result of drug companies promoting their products, through physicians, to people [...] for whom a powerful prescription may be unnecessary or even do more harm than good' (Moynihan and Henry, 2006). The latest pills are generally the most expensive, but not necessarily the most cost-effective.

Conclusions

In spite of the large amount of data demonstrating that progestins and OCs may benefit the majority of patients with symptomatic or recurring endometriosis, these medications are still addressed with scepticism and sometimes not even mentioned among effective therapeutic alternatives. According to experts in the field, the current medical treatment of endometriosis is not satisfactory, and there is a pressing need for novel therapeutics with better efficacy, tolerability and safety profiles (Guo, 2008). Unfortunately, it is taken for granted that an effective pharmacological therapy with such characteristics is lacking, when the available scientific information shows a different scenario. Progestins and OCs are blamed as inefficacious based on the fact that part of the women treated does not respond to therapy. Turned the other way round, it could be argued that the availability of safe and inexpensive therapeutics, which are ineffective in just a minority of patients, would reveal itself to be a dramatic benefit for a chronic disease such as endometriosis. Maintaining that progestins and OCs may be of a little value in the prevention of endometrioma recurrence and that the use of post-operative medications may cause unnecessary side effects and cost increase seems questionable in light of recent research findings. Indeed, women should be informed in an unbiased manner, as any misinformation may expose many of them to repeated surgery and a decrease in the probability of conception.

Medical treatment for endometriosis does not influence reproductive performance of infertile women. Therefore, pharmacological therapy must achieve two main objectives, i.e. relief of pain for prolonged periods and prevention of disease progression during the interval between conservative surgery and conception seeking. The available evidence supports the notion that, with regard to pain relief, OCs used continuously is a worthy option in women with peritoneal and ovarian lesions, whereas NETA appears to be the preferable compound in patients with rectovaginal disease. Concerning prevention of endometrioma recurrence, OCs are extremely effective whether used continuously or cyclically, as the mechanism of action seems to be ovulation inhibition.

Pharmacological therapy for endometriosis is inevitably a compromise. Not all women using progestins will be relieved from pain, not all will be satisfied with their treatment, not all will continue it and not all will avoid surgery. But at least two-thirds of them could substantially ameliorate their health-related quality of life, controlling the disease with marginal associated morbidity. This appears to be a major medical achievement, and as such should be regarded. So, should we still keep 'waiting for Godot'?

Authors' roles

P.Ve. conceived, drafted, and revised the article; E.S. and P.Vi. participated in conceiving the article, drafted a part and revised it; M.P.F. acquired the data and revised the article; P.G.C. and L.F. participated in conceiving the article and revised it; all the authors approved the final version of the article.

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