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METFORMIN LOWERS C-REACTIVE PROTEIN LEVELS AND IMPROVES THE MODIFIED BRIEF PAIN INVENTORY SCORES IN A WOMAN WITH ENDOMETRIOSIS – ASSOCIATED CHRONIC PELVIC PAIN: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Endometriosis is associated with low health-related quality of life and its incidence in the world is not decreasing, at least, in the developed economies. The aim of this case-report is to bring to the fore the beneficial effects of the insulin sensitizer, metformin, in endometriosis-associated chronic pelvic pain. Metformin lowered C-reactive protein levels and attenuated pain symptoms in a 48-year old woman diagnosed with endometriosis refractory to NSAIDs and hormone pills. The effect of metformin in endometriosis-associated chronic pelvic pain may be due to its anti-inflammatory and anti-oestrogenic effects and it warrants being further explored since endometriosis has no specific remedy at present.

Keywords: Endometriosis, Endometriosis-associated chronic pelvic pain, Metformin, Oestrogen, c-reactive protein, Pain scale.

INTRODUCTION

Endometriosis, an oestrogen-dependent process, is defined as the presence of endometrial-like tissue in the uterus (eutopic) or outside the uterus (ectopic) which induces a chronic inflammatory reaction. The condition can be present from premenarche to postmenopause but predominantly found in women of reproductive age from all ethnic and social groups [1-3]. The prevalence of endometriosis is 6-10% [4] but rises to 35-50% in women with infertility and chronic pelvic pain [3]. The associated symptoms which can impact negatively on general physical, mental and social well-being [5] include severe dysmenorrhea, deep dyspareunia, chronic pelvic pain, ovulation pain, cyclical or perimenstrual symptoms with or without abnormal bleeding, infertility, dysuria, constipation, dyschezia, adhesions, peritonitis, catamenial pneumothorax and chronic fatigue. Some affected women remain asymptomatic [1].

Patients with endometriosis-associated infertility undergoing in vitro fertilization respond with significantly decreased levels of all markers of reproductive process, resulting in a pregnancy rate that is almost one-half that of women with other indications for in vitro fertilization [6].

Genetics and endometriosis

Endometriosis may arise from the interplay between genetic variants and environmental factors [7]. Vast majority of familial cases of endometriosis involve the maternal lineage [8] in tandem with the fact that familial aggregation and twin studies have noted a higher risk of endometriosis among relatives [9-10]. Women with endometriosis have a tenfold increased risk of endometriosis in their first-degree relatives [11]. Risk factors of endometriosis include prolonged exposure to endogenous and exogenous oestrogen with dysregulation of progesterone signaling [12-14]. Genome-wide linkage studies [15-16] have identified loci on chromosome 7 p 15.2 and 10 q 26 that confer susceptibility to endometriosis.

Other risk factors

Autoimmune diseases [17] and serum polychlorinated biphenyl levels [18] have been observed as risk factors for endometriosis.

Pathogenesis

Retrograde menstruation, coelomic metaplasia, mullerianosis (rest or stem cells present from time of organogenesis) and immune alterations are favoured as being involved in the pathogenesis of endometriosis [19-21].

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Staging of endometriosis

Endometriosis may be staged surgically as follows
Stage 1 (minimal stage): Only superficial lesions plus possibly a few filmy adhesions
Stage II (mild stage): above plus some deep lesions being present in the cul-de-sac
Stage III (moderate stage): above plus endometriomas on ovary and more adhesions
Stage IV (severe stage): above plus large endometriomas and extensive adhesions

Recently, the endometriosis fertility index (EFI) has been observed as a validated endometriosis classification or staging system that predicts a clinical outcome. It is a validated clinical tool that predicts pregnancy rates after endometriosis surgical staging for those patients who attempt non-in vitro fertilization (non-IVF) conception [22-23] Novel research in imaging, biomarkers, histology and the human genome may provide useful information to develop future classification systems.

Endometriosis and cancer risk

There is an association between endometriosis and ovarian cancer risk [24] and hyperestrogenism is a relevant risk factor for the development of cancer from endometriosis [25].

Diagnosis

The preferred method of diagnosis is direct visualization of ectopic endometrial lesions (usually via laparoscopy) accompanied by histologic confirmation of the presence of at least two of the following features: hemosiderin-laden macrophages or endometrial epithelium, glands or stroma [26-27]. Gambone et al (2002) and Kennedy (2006) have asserted that laparoscopic diagnosis may not be necessary in all cases. While laparoscopic diagnosis is presently acclaimed to be the "gold standard'' for superficial endometriosis, magnetic resonance imaging may be more helpful in determining the extent of deep infiltrating (subperitoneal) lesions. Serum cancer antigen CA 125 may be useful as a marker of disease monitoring and treatment follow-up [28-29].

Differential diagnosis

In women with repetitive miscarriages, 85% may have endometriosis on diagnostic laparoscopy. Other causes of repetitive miscarriages to be ruled out in the differential diagnosis include hormonal abnormalities, ovulation defects and mucus cycle abnormalities. Chronic pelvic pain[30] frequently occurs secondary to non-gynaecologic conditions that must be considered in the evaluation of affected women. So, the differentials may include pelvic adhesions, serositis, ovarian cysts and ovarian cancer, colon cancer, adenomyosis, appendicitis, chlamydial genitourinary infections, diverticulitis, appendicitis, ectopic pregnancy, pelvic inflammatory disease, gonorrhea and urinary tract infections.

Pharmacotherapy of endometriosis

An ideal therapy should diminish the inflammation and underlying symptoms without negatively impacting fertility. No treatment currently exists for enhancing fecundity in women whose infertility is associated with endometriosis since all existing therapies are contraceptive [31]. In either a hypoestrogenic or a hyperandrogenic environment, endometriotic implants become atrophic [32] and this may be a pharmacologic basis for drug therapy. Medical therapy should last at least 6 months to allow for adequate regression of implants but it has a high recurrence rate, symptoms recurring in 75% of cases within 2 years. By comparison, surgical treatment may improve pregnancy rates and is the preferred initial treatment for infertility caused by endometriosis. Bilateral oophorectomy and hysterectomy or even presacral neurectomy may be deployed for intractable pain.

Present drugs for endometriosis include progestins, combined oral contraceptives, danazol that possesses androgenic activity, gonadotropin releasing hormones that cause profound hypoestrogenism but induce unpleasant menopausal symptoms. After failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs, empirical therapy with gonadotropin releasing hormone is appropriate [32]. Others include non-steroidal anti-inflammatory drugs, narcotic analgesics, pentoxifylline and COX_2 inhibitors. Therapeutic manipulation of the immune system with, for example, tumor necrosis factor-alpha inhibitors is now thought to be a prospective treatment.

Case-Report

A 48-year old Nigerian business-woman nullipara and a dual citizen of Canada and Britain, Mrs. M. P. was seen at Oseghale Oriaifo Medical Centre, Ekpoma, December 23rd, 2011 with a history of lower abdominal pains. She had papers documenting that she was diagnosed with stage II endometriosis 3 years earlier in Canada after laparoscopic examination and has been on non-steroidal anti-inflammatory drugs to which she was no longer responsive, hence the constant lower abdominal pains. She also complained of constipation, dyschezia and dyspareunia. There were also difficulties with sleep and concentration because of the pains. On examination, she was healthy-looking, afebrile. Her blood pressure was 130/80 mm.Hg and her Body Mass Index was 27.50 kg/m^2. Apart from some lower abdominal tenderness, there was nothing else of note.

The following laboratory and radiological tests were done to evaluate and rule out possible contributory causes:

1) Complete blood count, which was normal
2) Urinalysis, which was normal
3) Serum electrolytes and urea, which were normal
4) Malaria parasite test, which was negative
5) Widal test, which was negative
6) Fasting blood sugar, which was normal at 92 mg/dl

7) A routine chest X-ray, which revealed no abnormality
8) Haemoglobin genotype, which was rhesus positive
9) Abdominopelvic, vaginal ultrasound examinations, which showed light adhesions initially but became normal at 6 months
10) Barium enema which was normal
11) C-reactive protein levels using the immunoturbidimetric latex agglutination method (Cypress Diagnostics, Belgium) were done initially and after 3, 6 months.

The high initial C-reactive protein level of 19.20 mg/L was pointer that an inflammatory process was on, supporting the initial diagnosis of endometriosis with chronic pelvic pain (endometriosis-associated chronic pelvic pain). And for this patient in whom endometriosis was the suspected cause of the chronic pelvic pain, other non-gynecologic causes having being evaluated and ruled out, laparoscopic confirmation of diagnosis was deemed unnecessary who noted that a trial of medical therapy was justified if there was no indication for surgery such as the presence of a suspicious adnexal mass. Kennedy (2006) also noted that unnecessary laparoscopies should be prevented in patients, such as this case, who desire only symptom relief and that this approach does not adversely affect outcomes. Metformin was started for her at a dose of 1,500 mg/day in divided doses on 12th of January, 2012 [33].

Pain measurement

Pain measurement was done with a verbal rating scale and the Modified Brief Pain Inventory (www.britishpainsociety.org/members pain scales) initially, 3 and at 6 months.

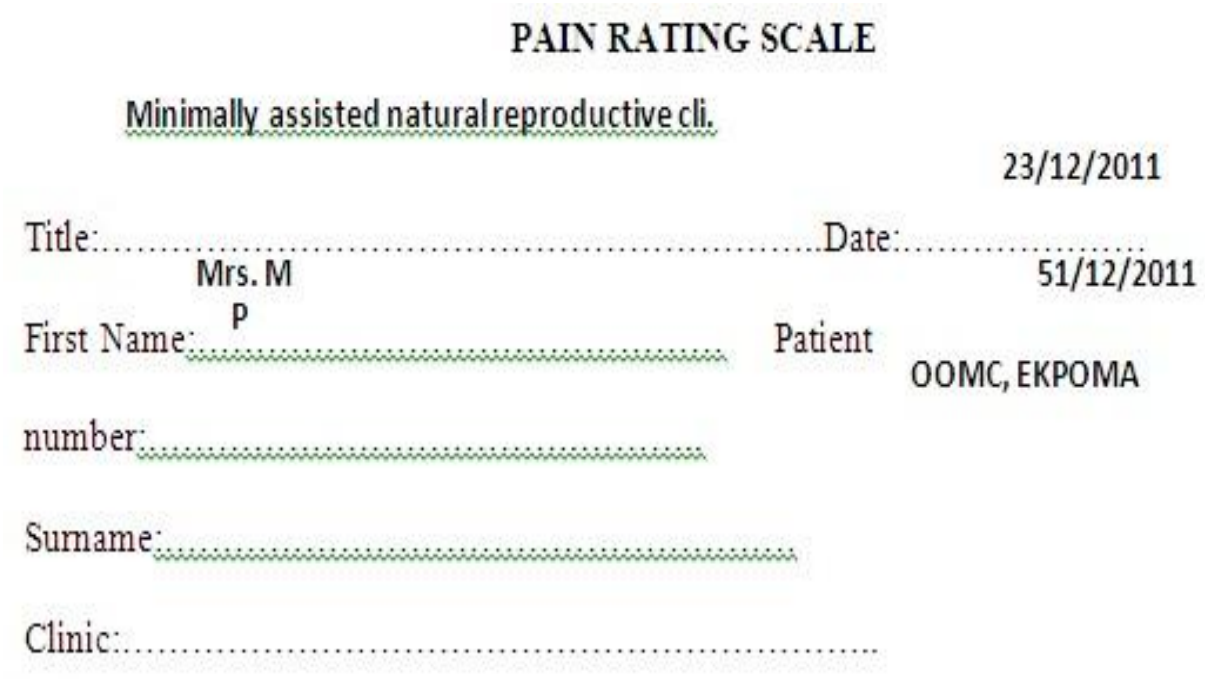
Table 1. Metformin significantly (*P < 0.05)reduced CRP level at 6 months. It also reduced the quality of pain on the verbal rating score and improved scores significantly on the brief pain inventory.

Table 1 shows that C-reactive protein (CRP) decreased to 2.80 ± 2.56 mg/L at 6 months from the initial 19.20 ± 3.45 mg/L. The verbal rating scale showed that the pain quality became mild at 6 months. The intensity of pain reduced from 10 to 2, distress due to pain from 10 to 2 and interference of pain with daily activities from 9 to 2 at 6 months. Percentage of relief from pain increased from 0% to 90% at 6 months (Figure 1). Difference of mean at 6 months compared to first month was significant (P < 0.05)

Also, at 6 months, patient no longer complained of constipation, dyschezia or dyspareunia. Her sleep and concentration also improved.

Table 1. Effect of metformin on c-reactive protein level and brief pain inventory score

	0	3	6 (Months)
C-Reactive (CRP) (mg/L)	19.20 ± 3.45	11.50 ± 4.20	2.80 ± 2.56*
Verbal Rating Scale	Severe	Mild	Mild
Average of modified brief pain inventory score	9.60	3.00	2.00*
Percentage relief (%)	0	80.00	90.00



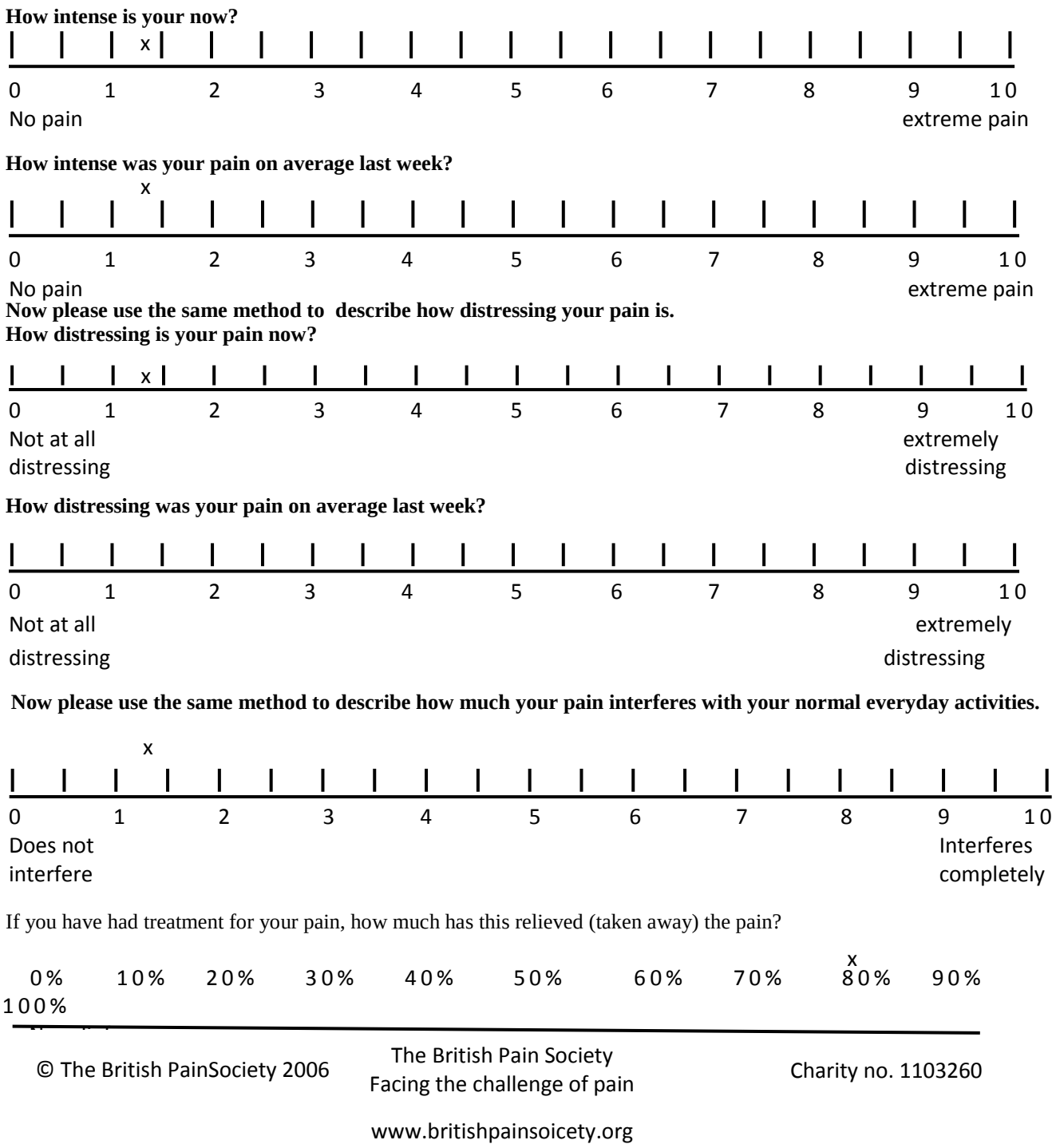


Figure 1. Metformin significantly (P < 0.05) improved scores in the Brief Pain Inventory at 6 months, decreasing the intensity and distress due to pain. It also decreased the interference of pain with daily activities and significantly relieved pain at 6 months.

DISCUSSION

Metformin significantly reduced the level of C-reactive protein and pain at 6 months in this patient with endometriosis-associated chronic pelvic pain. Previous report had noted that IL-6, which is the major upregulator of C-reactive protein gene [34] is attenuated by metformin. High C-reactive protein values are associated with pain due to chronic low-grade inflammation. The algogenic cytokines, nuclear factor-κB, tumor necrosis factor-alpha and transforming growth factor beta-1 are upregulated by C-reactive protein [35-38]. In turn, nuclear factor-κB and tumor necrosis factor-alpha upregulate C-reactive protein synthesis in the liver [39-40]. Metformin suppresses the

production of C-reactive protein [41] tumor necrosis factor-alpha [42] nuclear factor-κB [43] and transforming growth factor beta-1 [44]. This may be relevant to the action of metformin in attenuating the pain of endometriosis-associated chronic pelvic pain. Blockade of tumor necrosis factor-alpha inhibits pain responses centrally [45]. Anti-tumor necrosis factor-2 treatment has been found helpful for endometriosis-associated chronic pelvic pain buttressing the observation that endometriosis may be sustained by tumor necrosis factor-alpha [46]. Moreover, metformin's action in this patient could also be due to its antagonism of cyclooxygenase2 (COX2) [47-48] and algogenic prostanoids [49]. It may also suppress the algesic effects of the G-protein-coupled receptor (GPCR) agonist, bradykinin [50].

Results also indicate that there was non-progression of the endometriosis-induced fibrosis with metformin. Previous observations have indicated the beneficial effects of metformin in endometriosis in humans and animal models [51-53]. Transforming growth factor beta-1 (TGF beta-1) plays important role in the pathogenesis of endometriosis not only in its maintenance and propagation [54] but also as a powerful inducer of collagen synthesis [55]. Metformin has been reported to antagonize this TGF beta-1-induced fibrosis. Oestrogen in the liver enhances liver production of C-reactive peptide [56]. Metformin may also arrest the progression of endometriosis by reversing the hyperestrogenism and decreased progesterone signaling in the disorder [57-59]. Metformin decreases adipocyte aromatase activity and increases progesterone receptor expression [60]. The G-protein coupled estrogen receptor (GPER) is upregulated in ovarian endometriosis and pelvic inflammatory disease involving the ovary and may be a predictor of the main endometriosis-related symptoms [61]. Metformin may disrupt insulin-like growth factor-1 (IGF-1) – G-protein coupled estrogen receptor (GPER) signaling [62] by indirectly reducing levels of insulin, IGF-1 and other growth factors.

In conclusion, results indicate a role for metformin in endometriosis-associated chronic pelvic pain. Metformin which does not cause contraception and may be utilized as sole therapy for ovulation induction [63] stands to be an additional remedy for the endometriosis syndrome and warrants further evaluation.

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