Australasian Medical Journal AMJ 2010, 3, 12, 814-820

PPAR–gamma: a dagger in endometriosis

Amberkar MV[1], Meena Kumari K[1], Mor V[2], Semwal A[3], Adiga S [4]

[1,]Asst Professor, [4]Assoc Professor, Kasturba Medical College, Manipal University, Karnataka, India,
[2]Research Scholar, Manipal College of Pharmaceutical Sciences, Manipal University, India,
[3]Project Associate, BITS, Pilani, Hyderabad, India

REVIEW

Please cite this paper as: Amberkar MV, Meena K, Mor V, Semwal A , Adiga S .PPAR gamma: a dagger in endometriosis. AMJ 2010, 3, 12, 814-820. Doi 10.4066/AMJ.2010.261

Corresponding Author:
Dr Meena Kumari K
Dept of Pharmacology, Kasturba Medical College, Manipal-576104, Karnataka, India
Email@address-mini41178@yahoo.co.in

Abstract

Endometriosis is a debilitating gynecological disorder with an enigmatic pathogenesis. Current treatment strategy mainly involves surgery and medications, which provide only temporary relief. Endometriosis is associated with an abnormal inflammatory response, one of the recent pathogenesis is RANTES (regulated upon activation normal T-cell expressed and secreted) in endometriotic stromal cells, which is responsible for 70% of monocyte migration in the peritoneal fluid. This RANTES can be inhibited by the peroxisome proliferator activated receptor system. Thiazolidinediones (PPAR Gamma Agonists) exhibited the ability shown to suppress existing endometriotic lesions without suppressing ovulation. *In vivo* studies have shown some promising results which could be incorporated in humans. These results have promised new avenues of treatment emerging from older drugs. Since the existing conventional drugs have undesirable side effects, there is always a need for highly efficacious and better tolerated drugs acting through novel mechanisms of action. Hence, in this review we have highlighted the usage of a class of drugs commonly used to treat diabetes mellitus, which could also be used to treat endometriosis.

Key Words

Endometriosis, Infertility, Pain relief, PPAR-γ, Thiazolidinedione

Introduction

Endometriosis is a debilitating gynaecologic disorder with an enigmatic pathogenesis characterized by the ectopic presence of endometrial glands and stroma. According to recent reports the prevalence of endometriosis causing chronic pelvic pain[1] is 33%, compared to 6-10% observed a decade earlier.[2] It is one of the most important causes of dyspareunia, dysmenorrhoea, infertility and chronic pelvic pain seen in women still desiring to conceive.[3, 4] The recurrence rate for pelvic pain is as high as 75% in the 5-year follow up. The disease can distort the social, mental and economic well being of females significantly, including their ability to become pregnant.[5, 6]

Medical treatment is frequently needed because of high risk of recurrence after surgery**.** The current modalities of medical treatment for endometriosis are somewhat effective in relieving endometriosis-associated pain. However, the relief of pain appears to be relatively short term. In addition, the medications have many undesirable, unavoidable and sometimes severe side effects including climacteric syndrome and loss of bone density. Hence, more efficacious medicinal drugs, which are better tolerated, are required.[7]

A new treatment strategy for endometriosis is possibly peroxisome proliferator activated receptors (PPARs) agonists. The peroxisome proliferator-activating receptor γ (PPAR- γ) is a member of the nuclear hormone receptor super-family, which can modulate gene expression upon ligand binding. Studies have been shown to possess potent anti-inflammatory properties. PPAR-γ is activated by fatty acid derivatives, thiazolidinediones (TZDs) and certain non-steroidal anti-inflammatory drugs. TZDs have shown to be negative regulators of macrophage activation and inhibitors of monocyte inflammatory cytokines.[7] Currently, they are being used as insulin sensitizing drugs in the treatment of type 2 diabetes.

Pathophysiology

The most conspicuous feature of endometriotic lesions are their growth and inflammation, which are closely linked.[7] The growth of ectopic endometrium promotes overproduction of macrophages, excessive release of secretory products such as proinflammatory cytokines

and growth factors in the peritoneal fluid[7] which in turn, may result in further promotion of growth and resistance to apoptosis.[8] The increased production of cytokines mediates some of the symptoms of endometriosis such as pain and infertility in women of reproducing age.[9] The release of estrogen is responsible for growth of endometriotic tissue, thus the current medical treatment is aimed at suppressing ovarian steroidogenesis. Hence a gonadotrophin releasing hormone (GNRH) agonist is the most widely used treatment of endometriosis.[10, 11, 12] Current evidence supports the notion that the progression of endometriotic lesions is enhanced by an aberrant immune response in the peritoneal cavity of women with endometriosis.[13, 14, 15] It is uncertain whether the initial development of the disease is related to this inflammatory response. However, retrograde menstruation or iatrogenic seeding of the peritoneum with endometrial tissue will incite an inflammatory reaction. This results in the accumulation of activated macrophages, cytokines, chemokines and growth factors in the peritoneal fluid. Identification of functional aromatase enzyme in these lesions, has led strongly to the pathophysiological mechanisms — namely, inflammatory component and the estrogen dependency of endometriosis.[7] These processes are carried out by the immune-mediated production of prostaglandin endoperoxidase synthase-2 leading to high levels of prostaglandin E2, which in turn stimulates the aromatase II promoter in endometriotic stromal cells.[16] Recently, the expression of PRL-3[17], growth factor +405 C/G polymorphism[18], matrix metalloproteinases-7[19], differential regulation of Akt phosphorylation[20] and early menstrual characteristics[21] have been related to the different clinical stages and recurrence of endometriosis.[22] Chung et al[23] also reported that inhibition of CD36 dependent phagocytosis by prostaglandin E2 contributes to the development of endometriosis. Unfortunately, the lack of knowledge and incomplete understanding about the pathogenesis and pathophysiology are the major barriers in the treatment of endometriosis.

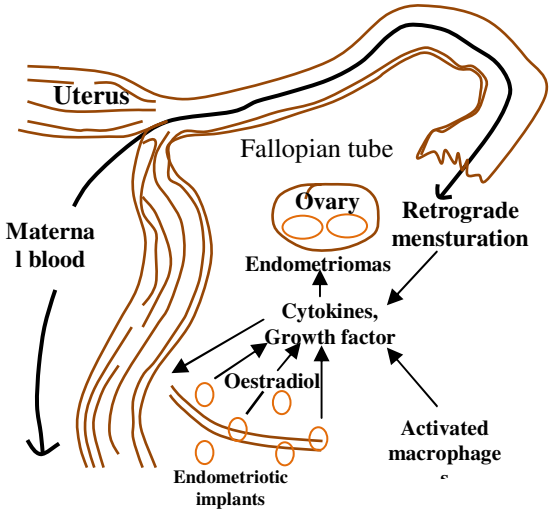

Figure.1 Schematic diagram of events occurring in the pelvis with retrograde menstruation

Therapeutic Strategies

The primary goal of medical treatment for endometriosis is to halt the growth and activity of endometriotic lesions.

Table- 1 Conventional therapy for endometriosis.[3]

Conventional Approaches	
Oral contraceptives	Ethinylestradiol plus progestagen
GnRH agonists	Leuprolide,Buserelin,Goserelin, Naferelin
Androgens	Danazol
Progestagens	Gestrinone,Medroxyprogesterone Acetate

Table-2 Hormonal and non hormonal approaches as new therapeutic strategies.[24,25]

Hormonal Approaches	
Gonadotropin releasing hormone antagonist	Cetrorelix
Aromatase inhibitors	Letrozole, Anastrozole
Progestogen agonists and Selective progesterone receptor modulators	Tanaproget, Mifepristone, Asoprisnil
Selective Estrogen Receptor modulators	Raloxifene, Genistein
Oral contraceptives	Combination of estrogen and progestagen
Non Hormonal Approaches	
Antiangiogenetics	Endostatin, TNP-470, Atorvastatin, Anginex, 2-methoxyestradiol
Immune-modulator	Interleukin-2, Interferon-α, Interleukin-12, Loxoribine, Levamisole, Imiquimod, Leflunomide, Bacillus Calmette-Guerin vaccine
COX-2 Inhibitors	Rofecoxib, Celecoxib, Indomethacin, Naproxene, Sulindac, Ibuprofen, NS398
TNF- α inhibitors	Human soluble TNF receptor type I, Etanercept
Other anti-inflammatory agents	Pentoxifylline, Melatonin, chemokine inhibitor NR58-3.14.3, factor nuclear kappa B inhibitors BAY 11-7085 and SN-50, caffeic acid phenethyl ester

Surgical treatment like radical excision of rectovaginal endometriosis has been reported to result in high rates of pain relief after long term follow up.[26] The current medical treatment strategy is effective in relieving the endometriosis associated pain for a relatively short period without overcoming the side effects of conventional therapy. For example, aromatase inhibitors exhibit a mechanism of action directed towards preventing recurrences rather than treating the disease, in addition they cause many undesirable and severe side effects. Hence, more efficacious and well tolerated treatment options are needed. In this context, β agonists, PPAR-γ agonists and COX-2 inhibitors represent the most promising agents and deserve greater medical attention. Immune modulating drugs have been studied as newer treatment options[27,28,29,30,31], including a recent successful study of recombinant human tumour necrosis factor binding protein in the baboon model of endometriosis.[32] In this review, we highlighted the precise role of peroxisome proliferator activated receptor gamma in endometriosis .[33]

Peroxisome Proliferators Activated Receptors

The peroxisome proliferator-activated receptors (PPAR) are ligand activated transcription factors that belong to the nuclear hormone receptor superfamily. They are structurally and functionally similar receptors, which have been cloned in Xenopus and are encoded by separate genes.[34] Three subtypes of PPARs are known to mediate a variety of functions that appear to be dependent upon their divergent distribution in the system.[35] These receptors are named PPAR-α, PPAR-β and PPAR-γ.[35] PPAR-γ, the most extensively studied receptor of the three subtypes, is predominantly detected in a variety of normal physiological functions (e.g. adipocyte differentiation) and in organs such as large intestine, kidney, liver, spleen, adrenal gland, small intestine, macrophages, endometrial epithelial and stromal cells and to a very limited extent in the muscle. It is also associated with several pathological conditions such as inflammatory lung disease[36], pulmonary arterial hypertension, atherosclerosis and cancer.[37,38,39]

PPAR-γ

PPAR-γ is a pleiotropic nuclear hormone receptor that binds to specific DNA response elements and may modulate gene expression either directly or indirectly, through competition with other transcription factors.[40] The highest expression of PPAR-γ is found in adipose tissue where it is principally involved in adipocyte differentiation.[41] Previous studies support the role for PPAR-γ ligands in regulating cell growth, apoptosis[42], inhibiting angiogenesis in human endometrial cells[43] and repressing inflammatory mediators.[44]

Mode of Action

When activated by ligand binding, PPAR-γ forms a heterodimer with another nuclear receptor retinoid X receptor (RXR) and then activates gene expression by binding to the PPRE (Peroxisome Proliferator Response Elements) in the regulatory region of the targeted genes.[45] This raises the question as to whether the co-administration of PPAR-γ and RXR ligands could further enhance the antiproliferative capability of either ligand. For the PPAR-γ /RXR heterodimers, the binding of the ligand of either receptor can activate the complex, yet binding of both ligands simultaneously is more potent. In addition, vitamin D receptor (VDR) and retinoic acid receptor (RAR), which may also be involved in the pathogenesis of endometriosis, also dimerize with RXR to direct repeat response elements, suggesting that RXR should play an obligatory role in endometriosis.[7] It would appear that different ligands can induce multiple changes in the structure of the receptor heterodimer, which subsequently result in the recruitment of a variety of modulator proteins (transcriptional co-activators or co-repressors). The interactions between the ligand, PPAR-RXR heterodimer, modulator proteins, and the transcription machinery affect the transcription initiation (up-regulation or down-regulation) and the synthesis of mRNA of the target genes.[35]

Role of PPAR –γ in Endometriosis

PPAR-γ is expressed in endometrial stromal cells and is thought to play a role in the pathogenesis of endometriosis related to regulation of genes involving proinflammatory cytokines including RANTES, (regulated upon activation of normal T-cell expressed and secreted). RANTES is a key which signals cytokines involved in the initiation of physiologic inflammation and is secreted by endometriotic cells.[46] It has been observed that the treatment of endometriosis with PPAR-γ ligand inhibits the RANTES promoter activity by 50% in endometriotic stromal cells.[44,46,47] Consistent with these reports, the administration of TZDs has been shown to induce regression of endometrial explants in rodents and baboon models of endometriosis[7]. These models showed histological changes similar to those seen in endometriotic lesions. PPAR-γ has also been shown to inhibit peritoneal inflammation and thereby preventing intra-abdominal adhesion formation.[40, 41, 42.]

PPAR-γ ligands have been shown to decrease aromatase enzyme activity in cultured human granulosa cells.[44,48] Most anti-inflammatory properties of PPAR-γ ligands are thought to arise through down-regulation of proinflammatory mediators in macrophages and by inhibition of the transcription factor nuclear factor-κB (NF-κB).[16] Since NF-κB appears to be constitutively activated in endometriotic cells, it appears to play a central role in the pathophysiology of endometriosis.[49] Rosiglitazone has also been found to ameliorate the immunological dysfunction seen with endometriosis and represents a novel alternate treatment.[16]

Drugs Modulating PPAR-γ Receptor

One of the most important group of PPAR-γ ligands is TZDs. These anti-diabetic agents are used in current clinical practice to treat type-2 diabetes, mainly to

reverse insulin resistance. However, the exact mechanism by which TZDs improve insulin sensitivity has not been fully established. The most commonly accepted view is that they exert their effects by selectively activating PPAR-γ, which in turn increases peripheral tissue sensitivity to insulin, especially in fat and muscle.[50] Thus; it seems that PPAR-γ may mediate, to a certain extent, the therapeutic effects of this class of compounds in treating insulin resistance.

In vitro and *in vivo* studies have implicated PPAR-γ ligands as potential modulators of inflammation-related diseases such as inflammatory bowel disease, psoriasis and rheumatoid arthritis. Their use in treating endometriosis is not so far-fetched.[51] Several *in vitro* studies which used TZDs on endometriotic cells led to their use in animal models of endometriosis.[43] To date there have been two published studies using TZDs in the rat model of endometriosis, with one revealing decreased induction of lesions[52] and the other showing regression of established endometriosis.[53] Since rodents do not have menses or develop spontaneous endometriosis, the ectopic autologous transplantation of uterine tissue in these models may not sufficiently replicate human endometriosis.[54] With this in mind, the baboon endometriosis model was established by intrapelvic seeding of menstrual eutopic endometrium on top of the pelvic organs.[51]

According to Lebovic et al 2007, the ability of rosiglitazone to significantly diminish endometriotic lesions were documented before treatment. The comparison groups were a placebo control, placebo treated baboons, and an active comparator or active control, GnRH-antagonist treated cohort. This study presents the first sub-human primate evidence that treatment with a TZD can reduce the surface area (~50% decrease in relative change compared to placebo) of induced peritoneal endometriosis.[51]

The staging laparoscopies were conducted at various times of the menstrual phase. However, by the final laparoscopy, three of the ganirelix baboons had serum progesterone levels significantly below 0.21ng/mL (below the sensitivity level of the assay), suggesting an ovarian suppressive effect, while no baboon in any other treatment group showed such low levels. Though, two rosiglitazone treated baboons displayed luteal phase levels of serum progesterone. There are only limited clinical studies on the reproductive influence of rosiglitazone and these are mostly confined to polycystic ovarian syndrome, where it has resulted in improved ovulation rate and a generous restoration of normal menstrual cycles. These studies support the notion that there were no untoward endocrinological effects of rosiglitazone versus the placebo group.[51]

Clinical data has cleared rosiglitazone from the increased hepatotoxicity risk that can be observed with other TZDs.[55] Rosiglitazone is classified as a pregnancy category C drug due to animal evidence of growth retardation in mid to late gestation, with 20 and 75 times the human dose.[56] However, no evidence of teratogenicity was noted in either preclinical or clinical trials. Rosiglitazone had no untoward effects on the growth and morphology of an *in vitro* rat embryo culture model despite concentrations as high as 10 times human peak plasma levels.[57] Studies on early human pregnancy have shown that rosiglitazone can be transported across the placenta in the late phase of the first trimester from 8–12 weeks[58], but in an *ex vivo* human perfusion model there was negligible transfer of rosiglitazone across the placenta.[59] This suggests that it may be safe to take the TZD until confirmation of pregnancy.

Altogether, this study suggests that the PPAR-γ agonist rosiglitazone may reduce the quantitative burden of established endometriotic lesions in baboons without affecting the menstrual cycle. Further studies in humans are required to determine if these results translate into diminished pelvic pain with rosiglitazone treatment.[51]

Though rosiglitazone has been given a black box warning label from the FDA due to an increased risk of cardiovascular side effects in heart failure patients, pioglitazone remains in the market and may be a viable substitute.

Ciglitazone was found to reduce the size of experimental endometriotic lesions in a rat model. This model suggested that a thiazolidinedione drug may be helpful in women with endometriosis.[53] Ciglitazone has been shown to significantly reduce aromatose enzyme expression in an IL-1β treated endometrial stromal cell line that harbours PPAR-γ.[60] Inhibitors of PPAR-α or activators of PPAR–γ have also been found to be beneficial in the treatment of inflammation associated with endometriosis. According to the study conducted by Wanichkul et al, PPAR- γ ligands enhance the expression of various cytokines such as IL-6, that could play a direct role in the aberrant growth of endometriotic lesions.[44]

Major hurdles in drug discovery for endometriosis

1. Pathogenesis of the disease is not completely understood yet.
2. Lack of new achievable drug targets.
3. Animal models for screening the treatments are not fully established to satisfy standards.
4. The research on endometriosis is underfunded compared to other diseases with high health care burdens.

This may be due to the practical difficulties of developing competitive research proposals on a complex and poorly understood disease, which affects only women.[61]

Limitations of review

Though endometriosis is a common gynaecological condition in women, we could retrieve few articles to support the view that PPAR-γ may prove to be a more effective for treating this condition in the near future. PPAR-γ may be a double edged sword possessing

beneficial as well as harmful effects such as increasing IL-6 levels. Major research has been done on existing animal models but due to the limited number of animal models available, it cannot be proven to be effective in humans. This necessitates conducting appropriately designed clinical trials to demonstrate that PPAR-γ agonists could be safer and more effective in treating endometriosis than the current treatments.

Conclusion

Activators of PPAR-γ pathways are potential candidates as a new therapeutic tool for treating endometriosis. It provides the opportunity to use TZDs to suppress existing endometriotic lesions without affecting ovulation. Further studies are required to assess ovarian function using TZDs and develop a reproductive safety profile. In regard to that, TZDs would be very convenient to administer. Furthermore, PPAR-γ agonists may be able to improve pelvic pain, relieve fertility related problems, and prevent recurrence without interfering with the menstrual cycle. Due to the diverse complexity in the pathophysiology of the disease, this new class of medication might be useful as an adjunct with conventional therapy. Hence, there is a great potential for therapeutic drug development research in the field of endometriosis.

References

1. Guo SW and Wang Y. The Prevalence of Endometriosis in Women with Chronic Pelvic Pain. Gynecol Obstet Invest. 2006; 62:121–130.
2. Eskenazi B and Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997; 24:235–258
3. Giudice LC and Kao LC. Endometriosis. Lancet. 2004; 364:1789–1799.
4. Farquhar C. Endometriosis. BMJ. 2007; 334:249–253.
5. Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological perspective. Hum Reprod Update. 2007; 13:395–404.
6. Bianconi L, Hummelshoj L, Coccia ME, Vigano P, Vittori G, Veit J, Music R, Tomassini A, D'Hooghe T. Recognizing endometriosis as a social disease: the European Union-encouraged Italian Senate approach. Fertil Steril. 2007; 88:1285–1287.
7. Yan Wu and Guo SW. Peroxisome proliferator-activated receptor-gamma and retinoid X receptor agonists synergistically suppress proliferation of immortalized endometrial stromal cells. Fertil Steril. 2009; 91:2142–2147.
8. Philip B and Clement MD. The pathology of endometriosis. Adv Anat Pathol. 2007; 14:241–260.
9. Taylor RN, Ryan IP, Moore ES, Homung D, Shifren JL, Tseng JF. Angiogenesis and macrophage activation in endometriosis. Ann NY Acad Sci. 1997; 828:194–207.
10. Henzel M and Kwei L. Efficacy and safety of nafarelin in the treatment of endometriosis. Am J Obstet Gynecol. 1990; 162:570–574.
11. Dlugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized placebo-controlled double blind study. Fertil Steril. 1990; 54:419–427.
12. Surrey ES and Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long term follow-up. Obstet Gynecol. 2002; 99:709–719.
13. Akoum A, Kong J, Metz C, Beaumont MC. Spontaneous and stimulated secretion of monocyte chemotactic protein-1 and macrophage migration inhibitory factor by peritoneal macrophages in women with and without endometriosis. Fertil Steril. 2002; 77:989–994.
14. Lebovic DI, Mueller MD, Hornung D, Taylor RN. Immunology of endometriosis. Immunol Allergy Clin N Am. 2002; 22:585–598.
15. Mueller MD, Mazzucchelli L, Buri C, Lebovic DI, Dreher E, Taylor RN. Epithelial neutrophil-activating peptide 78 concentrations are elevated in the peritoneal fluid of women with endometriosis. Fertil Steril. 2003; 79:815–820.
16. Lebovic DI, Mwenda JM, Chai DC, Mueller MD, Santi A, Fisseha S, D'Hooghe T. PPAR γ receptor ligand induces regression of endometrial explants in baboons:A prospective randomized placebo and drug controlled study. Fertility and Sterility. 2007; 88:1108–1119.
17. Ruan F, Lin J, Wu RJ, Xu KH, Zhang XM, Zhou CY, Huang XF. Phosphatase of regenerating liver-3: a novel and promising marker in human endometriosis. Fertil Steril. 2009 Dec 31.
18. Altinkaya SO, Ugur M, Ceylaner G, Ozat M, Gungor T, Ceylaner S. Vascular endothelial growth factor +405 C/G polymorphism is highly associated with an increased risk of endometriosis in Turkish women. Gynecol Obstet. 2009 Dec 30.
19. Matsuzaki S, Maleysson E, Darcha C. Analysis of matrix metalloproteinase-7 expression in eutopic and ectopic endometrium samples from patients with different forms of endometriosis. Hum Reprod. 2010; 25:742–750.
20. Cinar O, Seval Y, Uz YH, Cakmak H, Ulukus M, Kayisli UA, Arici A. Differential regulation of Akt phosphorylation in endometriosis. Reprod Biomed Online. 2009; 19:864–871.
21. Treloar SA, Bell TA, Nagle CM, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. Am J Obstet Gynecol. 2010; 202:534.e1-534.e6.

22. Laschke MW, Korbel C, Rudzitis-Auth J, Gashaw I, Reinhardt M, Hauff P et al. High-Resolution Ultrasound Imaging. A Novel Technique for the noninvasive in Vivo Analysis of Endometriotic Lesion and Cyst Formation in Small Animal Models. Am J Pathol. 2010; 176:585–593.
23. Chuang PC, Lin YJ, Wu MH, Wing LY, Shoji Y, Tsai SJ. Inhibition of CD36-Dependent phagocytosis by prostaglandin E2 contributes to the development of Endometriosis. Am J Pathol. 2010; 176:850–860.
24. Fedele L, Somigliana E, Frontino G, Benaglia L, Vigano P. New drugs in development for the treatment of endometriosis. Expert Opin Investig Drugs. 2008 ; 17:1187–1202.
25. Vercellini P, Somigliana E, Viganò P, Abbiati A, Barbara G, Crosignani PG. Endometriosis: current therapies and new pharmacological developments. Drugs. 2009; 69:649–675.
26. Tarjanne S, Sjoberg J, Heikinheimo O. Radical excision of rectovaginal endometriosis results in high rate of pain relief - results of a long-term follow-up study. Acta Obstet Gynecol Scand. 2010; 89:71–77.
27. Nothnick WB, Curry TE, Vemon MW. Immunomodulation of rat endometriotic implant growth and protein production. Am J Reprod Immunol. 1994; 31:151–162.
28. Ingelmo JM, Ouereda F, Acien P. Intraperitoneal and subcutaneous treatment of experimental endometriosis with recombinant human interferonalpha-2b in a murine model. Fertil Steril. 1999; 71:907–911.
29. Keenan JA, Williams-Boyce PK, Massey PJ, Chen TT, Bukoysky A. Regression of endometrial explants in a rat model of endometriosis treated with the immune modulators loxoribine and levamisole. Fertil Steril. 1999; 72:135–141.
30. D'Antonio M, Martelli F, Peano S, Papoian R, Borrelli F. Ability of recombinant human TNF binding protein-1 (r-hTBP-1) to inhibit the development of experimentally-induced endometriosis in rats. J Reprod Immunol. 2000; 48:81–98.
31. Hornung D, Chao VA, Vigne JL, Wallwiener D, Taylor RN. Thiazolidinedione inhibition of peritoneal inflammation. Gynecol Obstet Invest. 2003;55:20–24.
32. Barrier BF, Bates GW, Leland MM, Leach DA, Robinson RD, Propst AM. Efficacy of anti-tumor necrosis factor therapy in the treatment of spontaneous endometriosis in baboons. Fertil Steril. 2004; 81:775–779.
33. Tarjanne S, Sjoberg J, Heikinheimo O. Radical excision of rectovaginal endometriosis results in high rate of pain relief - results of a long-term follow-up study. Acta Obstet Gynecol Scand. 2010; 89:71–77.
34. Sharma S, Tandon Vr, Mahajan P, Koul I. Endometriosis: Treatment modalities. JK Science. 2007; 9:153–155.
35. Dreyer C, Krey G, Keller H, Givel F, Helftenbein G and Wahli W. Cell Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors, Cell. 1992; 68:879–887.
36. Liang G and Tabrizchi R. Peroxisome proliferator-activated receptor gamma as a drug target in the pathogenesis of insulin resistance .Pharmacology and Therapeutics. 2006; 111:145–173.
37. Becker J, Delayre-Orthez C, Frossard N, Pons F. Regulation of inflammation by PPARs: a future approach to treat lung inflammatory diseases? Fundam Clin Pharmacol. 2006; 20:429–447.
38. Fajas L, Auboeuf D, Raspé E, Schoonjans K, Lefebvre AM, Saladin R, et al. The organization, promoter analysis, and expression of the human PPAR gamma gene. J Biol Chem. 1997; 272:18779–18789.
39. Rosen ED and Spiegelman BM. PPAR gamma: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem. 2001; 276:37731–37734.
40. Ameshima S, Golpon H, Cool CD, Chan D, Vandivier RW, Gardai SJ et al. Peroxisome proliferator-activated receptor gamma (PPAR gamma) expression is decreased in pulmonary hypertension and affects endothelial cell growth. Circ Res. 2003; 92:1162–1169.
41. Semple RK, Chatterjee VK, O'Rahilly S. PPAR gamma and human metabolic disease. J Clin Invest. 2006; 1 16:581–589.
42. Tontonoz P, Hu E and Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. Cell.1994; 79: 1147–1156.
42. Yee LD, Sabourin CL, Liu L, Li HM, Smith PJ, Seewaldt V et al. Peroxisome proliferator-activated receptor gamma activation in human breast cancer. Int J Oncol. 1999; 15:967–973.
43. Peeters LL, Vigne JL, Tee MK, Zhao D, Waite LL, Taylor RN. PPAR gamma represses VEGF expression in human endometrial cells: implications for uterine angiogenesis. Angiogenesis. 2005; 8:373–379.
44. Wanichkul T, Han S, Huang RP, Sidell N. Cytokine regulation by peroxisome proliferator activated receptor gamma in human endometrial cells.Fertil Steril. 2003; 79:763–769.
45. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K et al. The nuclear receptor superfamily: the second decade. Cell. 1995; 83:835– 839.
46. Akoum A, Lemay A, Maheux R. Estradiol and interleukin-1 beta exerta synergistic stimulatory effect on the expression of the chemokine regulatedupon activation, normal T cell expressed, and secreted in endometriotic cells. J Clin Endocrinol Metab. 2002; 87:5785–5792.
47. Pritts EA, Zhao D, Ricke E, Waite L, Taylor RN. PPAR-

gamma decrease endometrial stromal cell transcription and translation of RANTES in vitro. J Clin Endocrinol Metab. 2002; 87:1841–1844.

48. Fan W, Yanase T, Morinaga H, Mu YM, Nomura M, Okabe T et al. Activation of peroxisome proliferator activated receptor gamma and retinoid X receptor inhibits aromatase transcription via nuclear factor kappa B. Endocrinology. 2005; 146:85–92.
49. Guo SW. Nuclear factor-kappaB (NF-kappaB): an unsuspected majo rculprit in the pathogenesis of endometriosis that is still at large? Gynecol Obstet Invest. 2006; 63:71–97.
50. Moller DE. New drug targets for type 2 diabetes and the metabolic syndrome. Nature. 2001; 414: 821–827
51. Lebovic DI, Mwenda JM, Chai DC, Mueller MD, Santi A, Fisseha S et al. PPAR γ receptor ligand induces regression of endometrial explants in baboons: A prospective randomized placebo and drug controlled study. Fertility and Sterility. 2007; 88:1108–1119.
52. Demirturk F, Aytan P, Caliskan AC, Aytan P, Koseoglu DR. Effect of peroxisome proliferator actiated receptor gamma agonist rosiglitazone on the induction of endometriosis in an experimental rat model. J Soc Gynecol Investig. 2006; 13:58–62.
53. Lebovic DI, Kir M, Casey CL. Peroxisome proliferator activated receptor gamma induces regression of endometrial explants in a rat model of endometriosis. Fertil Steril. 2004; 82:1008–1013.
54. Vernon MW and Wilson EA. Studies on the surgical induction of endometriosis in the rat.Fertil Steril. 1985; 44:684–694.
55. Lebovitz HE, Kreider M, Freed MI. Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care. 2002; 25:815–821.
56. Brunmair B, Staniek K, Gras F, Scharf N, Althaym A, Clara R et al. Thiazolidinediones, like metformin, inhibit respiratory complex I. Diabetes. 2004; 53:1052–1059.
57. Chan LY and Lau TK. Effect of rosiglitazone on embryonic growth and morphology: a study using a whole rat embryo culture model. Fertil Steril. 2006; 86:490–492.
58. Chan LY, Yeung JH, Lau TK. Placental transfer of rosiglitazone in the first trimester of human pregnancy. Fertil Steril. 2005; 83:955–958.
59. Holmes HJ, Casey BM, Bawdon RE. Placental transfer of rosiglitazone in the ex vivo human perfusion model. Am J Obstet Gynecol. 2006; 195:1715–1719.
60. Kavoussi SK, Arosh JA, Lee J, Banu SK, Lebovic DI. PPAR-gamma ligand activation decreases p450 aromatase gene expression in human endometriotic epithelial and stromal cells in vitro. Fertil Steril. 2009; 92:S12.
61. Rogers PA, D'Hooghe TM, Fazleabas A, Gargett CE, Giudice LC, Montgomery GW et al. Priorities for Endometriosis Research: Recommendations from an International Consensus Workshop. Reproductive Sciences. 2009; 16:335–346.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance of Isabelle Cameron, Department of Biological Sciences, The University of Southern Queensland, Toowoomba, Australia. with the proofreading of this manuscript.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interest

FUNDING

Nil