Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

# Reviewing the role of progesterone therapy in endometriosis

Abdul Kadir Abdul Karim, Mohamad Nasir Shafiee, Nor Haslinda Abd Aziz, Mohd Hashim Omar, Nur Azurah Abdul Ghani, Pei Shan Lim, Reena Rahayu Md Zin & Norfilza Mokhtar

**To cite this article:** Abdul Kadir Abdul Karim, Mohamad Nasir Shafiee, Nor Haslinda Abd Aziz, Mohd Hashim Omar, Nur Azurah Abdul Ghani, Pei Shan Lim, Reena Rahayu Md Zin & Norfilza Mokhtar (2018): Reviewing the role of progesterone therapy in endometriosis, Gynecological Endocrinology, DOI: 10.1080/09513590.2018.1490404

**To link to this article:** https://doi.org/10.1080/09513590.2018.1490404

Published online: 25 Jul 2018.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2018.1490404

Taylor & Francis
Taylor & Francis Group

REVIEW



# Reviewing the role of progesterone therapy in endometriosis

Abdul Kadir Abdul Karim[a], Mohamad Nasir Shafiee[a], Nor Haslinda Abd Aziz[a], Mohd Hashim Omar[a], Nur Azurah Abdul Ghani[a], Pei Shan Lim[a], Reena Rahayu Md Zin[b] and Norfilza Mokhtar[c]

[a]Department of Obstetrics & Gynaecology, Universiti Kebangsaan Malaysia Fakulti Perubatan, Pusat Perubatan UKM, Kuala Lumpur, Malaysia; [b]Department of Pathology, Universiti Kebangsaan Malaysia Fakulti Perubatan, Pusat Perubatan UKM, Kuala Lumpur, Malaysia; [c]Department of Physiology, Universiti Kebangsaan Malaysia Fakulti Perubatan, Pusat Perubatan UKM, Kuala Lumpur, Malaysia

**ABSTRACT**

Endometriosis is a benign, chronic inflammatory condition characterized by the presence and growth of endometrial implants outside the uterine cavity. The cause of endometriosis is multifactorial. It is due to the diversity of hypothesis and plausibility of hormonal alterations which could play a major role. Evidence has shown that progesterone resistance is a key factor for endometriosis sufferers. Medical therapy can avoid surgical intervention, which may lead to a reduced in ovarian reserve, and its effects of earlier menopause and reduced fecundity. Progesterone receptor isoform has provided new insight as the potential treatment. Progestin, anti-progestin and selective progesterone receptor modulators usage, which target these receptors, could avoid hypo-estrogenic side effects, which can be debilitating. Numerous types of these medications have been used on and off labeled to treat endometriosis with varying success. This review aims to consolidate series of clinical trials using progestins in endometriosis.

**ARTICLE HISTORY**
Received 29 January 2018
Revised 4 June 2018
Accepted 14 June 2018
Published online 20 July 2018

**KEYWORDS**
Endometriosis; progesterone; progesterone receptor; progestin; progesterone receptor isoform

## Introduction

Endometriosis is a benign condition which is characterized by chronic inflammation and the growth of endometrial cells outside of the uterine cavity [1]. It commonly involves the peritoneum and pelvic organs and rarely involves extra-abdominal sites [2]. Accidental findings of ectopic endometrial tissues during laparoscopy in an asymptomatic woman may suggest that endometriosis is regarded as a normal process. This disease is considered pathological when there are symptoms related to it such as chronic abdominal pain, dysmenorrhea and dyspareunia [3].

The etiology is multifactorial [4,5]. Hormonal alterations may influence the propagation of endometriosis, which is a viewed as an estrogen-dependent disorder [6]. An important finding was that there is an increased expression of aromatase enzyme and a decrease expression of 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) [7] in endometriotic tissue when compared to eutopic endometrium. As a result there is a higher local estradiol (E2) bioavailability. This will stimulate the production of prostaglandin E2 (PGE2) which then further stimulates aromatase activity [8]. The main aim of this review is to update the latest clinical pharmacological studies in endometriosis targeting progesterone receptors. Other pharmacological methods which target these receptor which are progesterone antagonist and selective progesterone receptor modulator (SPRM) had been evaluated in a recent Cochrane review [9].

## Methodology

Available evidence for the role of progesterone receptors and its isoforms in endometriosis was reviewed. A systematic search was done using Medline by Ovid using key words 'endometriosis' AND the related progestin either 'norethisterone', 'medroxyprogesterone', 'cyproterone', 'dienogest', 'dydrogesterone', 'etonogestrel', and 'levonogestrel'. Recent clinical trials articles were taken from the last five years from 2013 till present and search was performed in January 2018. Original studies of clinical trials using the progestins in a cohort of endometriosis patients were selected and reviewed. Relevant clinical papers cited in the clinical and review articles were also reviewed to ensure earlier important evidence was not omitted. Related articles concerning the subject were also scrutinized for completeness.

## Progesterone effect in normal endometrial function

Progesterone is a steroid hormone. During the menstrual cycle it is secreted by the corpus luteum after ovulation as the endometrium enters secretory phase. This counteracts the effect of estrogen, which proliferates the endometrium and stimulates tissue remodeling until pregnancy occurs or until menstrual shedding. Other effect of progesterone on endometrium is to stimulate the expression of enzyme 17HSDB2 in epithelial cells. During the luteal phase this enzyme catalyzes the conversion of biologically active estrogen (E2) to less estrogenic steroid, estrone (E1) and testosterone to androstenedione [10]. This effects is however is being block by local endogenous E2 in endometriotic lesions. As a result there is incomplete transition of endometrium from proliferative to secretory phase. Consequently this may enhance the survival and implantation of refluxed endometrium. Conversion of potent estrogen E2 to E1 in the secretory phase endometrium is regarded as a critical protective mechanism against estrogen-induced growth [2].

CONTACT Norfilza Mokhtar norfilza@ppukm.ukm.edu.my Department of Physiology, Universiti Kebangsaan Malaysia Fakulti Perubatan, Pusat Perubatan UKM, Jalan Yaakob Latif, Bandar Tun Razak, Kuala Lumpur, 56000 Malaysia

## Human progesterone receptors

The human progesterone receptor (PR) gene was localized to 11q22–q23 [11]. Progesterone effects are mediated via intracellular PR which are expressed from a single gene as two protein isoforms. These are progesterone receptor A (PR-A) and progesterone receptor B (PR-B) [12] which are a 94-kDA and a 114-kDa protein respectively with the later containing an additional 164 amino acids at its amino-terminal [13–15]. These receptors may arise from either initiation of translation from alternative sites in the same mRNA or by transcription from alternative promoters in the same gene [12,16]. PR-A may act as a transpressor of PR-B activity in certain cells for specific promoters [17].

## Roles of progesterone receptors in endometriosis

Progesterone resistance is one of the cause of endometriosis. It is explicable by the extremely low PR levels in endometriotic tissue. In normal endometrium, levels of PR-A and PR-B progressively increase during the proliferative phase, peaking immediately before ovulation, and diminish after ovulation, suggesting that E2 stimulates PR levels [18]. In contrast endometriotic lesions demonstrate a reduced PR-A expression compared to eutopic endometrium and an absence of PR-B. This is likely a contributing mechanism where progesterone does not trigger the expression of 17BHSD2 and subsequent metabolism of E2 to E1 [19,20]. Moreover, endometrial expression profiling has documented dysregulation of progesterone-responsive genes in the luteal phase [19,21,22].

Drugs that have an effect on PR activity includes progestin, anti-progestin and SPRM.

## Types of progesterone-based therapy

Progestins are synthetic compound that mimic the effect of progesterone. There is a wide spectrum of these steroids derived from different parent compound. Progestin can be classified according to their chemical structure, chemical classification or route of administration. An overview of the types of progestin by their route of administration is illustrated in Table 1. A summary of the recent trials of the various agents are listed in Table 2 (oral progestins) and Table 3 (parenteral progestins).

### *Oral progestins*

#### *Norethisterone acetate (NETA)*

Norethisterone acetate (NETA) is a C-19-nortestosterone derivative. Several randomized controlled trials have shown it to be effective in endometriosis related pelvic pain [23,24]. More recently a study on patients with rectovaginal endometriosis (RVE) has shown almost 70% of 61 patients were satisfied with using up to 5 mg/day for five years [25]. Intensity of chronic pelvic pain, deep dyspareunia and dyschezia had also shown improvement. A study treating unilateral endometrioma showed a 37% reduction in volume after six months, however the sample size was only 6 [26]. There was a trial using NETA as addback therapy in combination with 17β-estradiol for GnRH agonist therapy after laparoscopy for endometriosis which showed it to be effective and tolerable for prevention of pelvic pain recurrence [27]. NETA has the advantage of controlling uterine bleeding and also has a positive effect on calcium metabolism, while it lacks the negative effect on lipoprotein profile [24]. NETA has a low cost and a good pharmacological profile, as such it is a good option for long-term oral treatment of pelvic endometriosis.

**Table 1.** Classification of progestin by route of administration.

| Route | Examples |
|---|---|
| Oral | Norethisterone, Medroxyprogesterone, Cyproterone, Dienogest, Dydrogesterone |
| Intramuscular | Medroxyprogesterone |
| Subcutaneous | Etonogestrel |
| Intrauterine | Levenogestrel |

#### *Medroxyprogesterone acetate (MPA)*

Medroxyprogesterone acetate (MPA) is a C-21 progestogen derivative with moderate androgenic activity and minor effects on lipoprotein metabolism. It has been compared to placebo and GnRH agonist (Nafarelin). It has a greater efficacy in alleviating the pain and improving the quality of life against placebo and equal effectiveness to GnRH agonist [28]. It has also has been shown to be equally as effective as GnRH analog for reducing pain and improving health-related quality of life [24]. There has been no recent studies using MPA as treatment of endometriosis. There is however, a trial using it as add back therapy in combination with estradiol valerate (2.5 mg MPA and 1 mg estradiol valerate) for post-operative GnRH therapy. In this trial of 107 women, it could effectively ameliorate hypoestrogenic side effects and simultaneously maintain the therapeutic response of GnRH agonist treatment [29]. MPA remains a good option for treatment despite its androgenic activity as it has a low cost.

#### *Cyproterone acetate (CPA)*

Cyproterone acetate (CPA) is a C-21 progestogen derivative, which is mainly anti-androgen and has a weak progestational activity. It has been compared to oral contraceptive (desogestrel and ethinyl estradiol) for treatment of endometriosis [30] and both the study groups was found to be equal in effectiveness for reduction in pain, sexual satisfaction and improvement in quality of life. CPA was also used with estradiol for the treatment of symptomatic RVE, however only 62% of the study group was satisfied with the treatment. Our search did not reveal any recent clinical studies using CPA alone or in combination for endometriosis. The lack of published trials could be due to its weak progestational activity.

#### *Dienogest (DNG)*

Dienogest (DNG) is a C-10 nortestosterone progestogen derivative, which has an anti-androgenic activity and a weak antigonadotropic effect. DNG improves progesterone resistance in endometriotic expression of estrogen receptor β (ERβ) and estrogen recetpor α (ERα) [31].

Dienogest has shown to be effective in controlling endometriosis related pelvic pain and having good tolerability in patients [32–39]. The optimal dose for DNG for treatment of endometriosis is 2 mg once daily, as it improves endometriosis associated symptoms such as dysmenorrhea, premenstrual pain and diffuse pelvic pain and because the percentage of irregular bleeding is statistically lower [33,40].

Dienogest has also been compared to GnRH agonist (Buserelin and Leuprolide acetate) and was found to have a

**Table 2.** Recent clinical trials using oral progestin for endometriosis.

| Oral progestin | Author | Year | Patients | Cohort | Intervention | Type | Primary outcome |
|---|---|---|---|---|---|---|---|
| NETA | Morotti et al. [25] | 2017 | *103* | Women with pain caused by rectovaginal endometriosis | NETA alone (2.5 mg/day up to 5 mg/day) for five years | Retrospective | Degree of satisfaction with treatment |
| | Taniguchi et al. [26] | 2017 | *6* | Women with unilateral ovarian endometrioma | NETA (5 mg/day every day for at least six months) | Prospective | Size of endometrioma |
| | Lee et al. [27] | 2016 | *64* | Women of reproductive-aged who underwent laparoscopic surgery for endometriosis | Post-operative GnRHa plus 17β-estradiol and NETA vs dienogest for six months | Prospective | Prevention of pelvic pain recurrence after laparoscopic surgery for endometriosis |
| MPA | Tsai et al. [29] | 2016 | *107* | During postoperative GnRHa treatment, women were prescribed add-back therapy | Oral combination tablet; estradiol valerate (1 mg) and MPA (2.5 mg) for 20 weeks OD (low dose) vs BD | Prospective | Whether low-dose add-back therapy can also effectively relieve the hypoestrogenic side effects |
| Dienogest | Maiorana et al. [38] | 2017 | *132* | Women with a surgical diagnosis of endometriosis or a clinical/instrumental diagnosis of endometriosis | Dienogest 2 mg OD for no more than 30 days | Observational | Improvement of pain |
| | Lang et al. [39] | 2018 | *255* | Chinese women aged 18–45 years with laparoscopically diagnosed endometriosis | About 2 mg dienogest vs placebo OD for 24 weeks | RCT | Improvement of pain |
| | Leornado-Pinto et al. [42] | 2017 | *30* | Women with sonographic diagnosis of DIE | Dienogest 2 mg/day for 12 months | Prospective | Improvement of pain |
| | Yamanaka et al. [43] | 2017 | *126* | Women who underwent laparoscopic resection of uterosacral ligaments with DIE | Postoperative dienogest 2 mg/day vs no medication. | Retrospective | Occurrence of pelvic pain and endometrioma |
| | Seo et al. [44] | 2017 | *60* | Women who underwent conservative surgery for endometriomas | Postoperative dienogest 2 mg/day for at least 12 months | Prospective | Effects on BMD |
| | Ebert et al. [45] | 2017 | *120* | Adolescents aged 12–18 years with clinically suspected or laparoscopically confirmed endometriosis | Dienogest 2 mg/day for 52 weeks | Prospective | Effects on BMD |
| Dydrogesterone | Zou et al. [51] | 2013 | *81* | Women 18–50 years with stage III or IV endometriosis given post-operative GnRHa 3.6 mg by subcutaneous injection once every 28 days for a total of three times | GnRHa only group vs GnRHa plus 0.5 mg estradiol valerate and 5 mg dydrogesterone orally every day vs GnRHa plus 1 mg estradiol valerate and 10 mg dydrogesterone orally every day | Prospective | Lowest effective dose of combined estrogen and progestogen add-back therapy during post-operative GnRHa treatment for endometriosis |

NETA: Norethisterone acetate; MPA: Medroxyprogesterone acetate; GnRHa: Gonadotrophin releasing hormone analog; OD: once daily; BD: twice daily; DIE: deep infiltrating endometriosis; BMD: Bone mineral density; RCT: randomized control trial.

lower adverse effect profile [32,36]. The main side effect appears to be bleeding problems in the first three months of treatment [36]. However, there is a progressive decrease in adverse effects and bleeding irregularities, and also decrease in pain for at least six months after cessation of treatment [37]. A comparison against placebo or leuprorelin depot had also showed a significant improvement in endometriosis related symptoms with comparable effectiveness to GnRH agonist treatment [34,35].

Dienogest has a positive outcome in terms of reducing the size of lesions of deep endometriosis (rectosigmoid and bladder endometriosis) after 10/11 months of use, while the relief of subjective symptoms was immediate [41].

More recently studies has shown consistent results that DNG is effective in controlling pain due to deep infiltrating endometriosis [42]. It also significantly reduces the occurrence rate of endometrioma when given post-operatively after laparoscopic resection of deep infiltrating endometriosis [43]. However long-term postoperative DNG treatment for endometriosis may have an adverse effect on bone mineral density in reproductive woman [44]. Similar finding was also found in a cohort of adolescents 12–18 years old where decreased of lumbar bone mineral density was found after 52 weeks of usage [45]. To date, DNG has been well investigated on multiple aspects. It has consistently shown to be effective for pain, and reduced endometrioma recurrence. However, there is a persistent concern on BMD effect, especially among adolescents.

### *Dydgrogesterone*

Dydrogesterone is a synthetic derivative of retroprogesterone, a stereoisomer of progesterone, with an additional double bond between carbon 6 and 7. Dydrogesterone is a highly selective progestin, which resembles progesterone mainly in its progestogenic effects and less in its andorgenic, anti-androgenic, glucocorticoid and anti-glucocorticoid effects. Due to its retrostructure, it binds almost exclusively to the PR. It has a strong agonistic activity for PR-B and only a weak agonistic activity for PR-A. This selectivity results in minimal or no unwanted side-effects [46,47].

Studies have used dydrogesterone between 10 and 60 mg/day for various duration per cycle over one to six months [48–50]. The majority of women became symptom-free or experienced a significant reduction in the number/severity of symptoms. More recently, dydrogesterone has also been used in doses of 5 to 10 mg in combination with estradiol valerate as add-back therapy for postoperative GnRH analog in moderate to severe endometriosis. A combination of 0.1 mg estradiol valerate/5 mg

**Table 3.** Recent clinical trials using parentral progestin for endometriosis.

| Parentral progestin | Author | Year | Patients | Cohort | Intervention | Type | Primary outcome |
|---|---|---|---|---|---|---|---|
| Depot | Carr et al. [54] | 2014 | *252* | Women with endometriosis-associated pain | Elagolix (150 mg every day, 75 mg BD) vs subcutaneous DMPA | RCT | Effects on BMD |
| | Cheewadhanaraks et al. [55] | 2013 | *61* | Women with symptomatic endometriosis, who had been treated with DMPA for 15 months and were satisfied with the treatment | DMPA for 15 months | Questionnaire | Recurrence rates of endometriosis-associated pain after long-term intramuscular DMPA |
| IUS | Li et al. [66] | 2017 | *102* | RVE patients who underwent transvaginal partial excision | LNG-IUS insertion vs oral contraceptive drospirenone/ethinylestradiol 3 mg/30 μg administration | Retrospective | Pain, sexual function and quality of life |
| | Chen et al. [67] | 2017 | *80* | Women with endometriomas undergoing laparoscopic cystectomy followed by six cycles of gonadotropin-releasing hormone agonist treatment | Receive a LNG-IUS vs did not receive | RCT | Prevention of postoperative endometrioma recurrence |
| | Kim et al. [68] | 2018 | *28* | Women who had undergone surgery for endometriosis followed by six cycles of GnRHa treatment | LNG-IUS | Prospective | Prevention of endometriotic cyst recurrence |
| | Cho et al. [69] | 2014 | *99* | Women with endometriomas | Postoperative LNG-IUS placement vs postoperative cyclic, low-dose, monophasic, OCs | Retrospective | Comparing the efficacy of postoperative use of LNG-IUS with oral contraceptives for preventing endometrioma recurrence |
| | Morelli et al. [70] | 2013 | *92* | Women undergoing surgery for endometriosis | Subsequent treatment by estradiol valerate + dienogest vs LNG-IUS | Prospective | Pain relapse and disease recurrence rate at 12 and 24 months |

NETA: Norethisterone acetate; MPA: Medroxyprogesterone acetate; GnRHa: Gonadotrophin releasing hormone analog; OD: once daily; BD: twice daily; DIE: deep infiltrating endometriosis; BMD: Bone mineral density; RCT: Randomize control trial.

dydrogesterone can reliably relieve pain symptoms, reduce bone mass loss, alleviate menopausal symptoms, improve quality of life, minimize overall adverse effects, improve patient compliance and prolong GnRH agonist treatment duration [51]. Dydrogesterone is a good option due to its high selectivity to PR which minimizes adverse effects.

### Depot

Depot injections of MPA are effective in suppressing symptoms attributed to endometriosis. Depot MPA (DMPA) has been studied in doses of 150 mg intramuscularly and 104 mg subcutaneously every three months. Comparison was against a combination of oral contraceptive with Danazol and against GnRH agonist (leuprolide acetate), respectively [52,53]. It was shown to be better than combined oral contraceptive and equivalent to GnRH agonist for the control of pain.

Depot MPA was more recently compared against GnRH antagonist (elagolix) for the treatment of endometriosis, which showed no difference in the reduction of pain symptoms. There was demineralization of bone and hypoestrogenic side effects were found in the GnRH antagonist group while bleeding problems were more frequent in the DMPA group [54]. DMPA attained good pain relief with minimal side effects (bloating and spotting). Its optimum interval of administration should be every three months. DMPA was also found to have minimal impact on bone mineral density over a 24-week period and had similar efficacy on endometriosis-associated pain when compared to oral GnRH antagonist [54]. Recurrence rate of pain after discontinuation of DMPA was up to 50% at five years in another recent trial [55]. DMPA should be considered for its advantages of 3 monthly interval in selected patients of endometriosis.

### Subdermal implants

Subdermal implants is marketed as Implanon, uses a single rod containing Etonogestrel 68 mg with a life span of three years. Etonogestrel is a 19-nortestosterone derivative. It is a safe and well-tolerated alternative for treatment of endometriosis besides being non-patient dependent contraception. It has been found equally effective compared to DMPA in pain relief in 12 months use with the significant reduction in the first three months [56]. This long-term progestogen delivery method has also been proven to reduce dysmenorrhea [57]. As such Etonogestrel should be considered as an alternative in treating endometriosis associated pain. Etonogestrel should be preferred to DMPA because it has not shown to have any effect on BMD [58] and also in patients with a high body mass index (BMI) and in women with a desire for pregnancy. There has been no recent clinical study assessing Etonogestrel for endometriosis.

### Intrauterine systems

A new aspect for treatment of endometriosis is the intrauterine administration of progestins. Levonogestrel (LNG) intrauterine system (IUS)/Mirena releases 0.02 mg of LNG per day with a life span of five years. LNG is a gonane (with an ethyl group

position of C-13) derived from 19-nortestosterone that has an anti-estrogenic and androgenic action on the endometrium.

Besides improvement of pelvic pain [59], anti-proliferative effects in the ectopic endometrium have been shown [60]. Findings of reduction in pain were also confirmed by prospective observational studies [61,62]. Up to 56% of patients who maintained the device till 3 years had a significant reduction in dysmenorrhea scores [63]. LNG-IUS had been compared with GnRH agonists to treat endometriosis related pelvic pain and was found to have a stronger pain-reduction effect [64]. Bleeding and pain were more frequently related to LNG-IUS compared to GnRH agonist, however LNG-IUS avoids the hypoestrogenic state symptoms and has a better lipid profile [65].

LNG-IUS has also been suggested to be effective against RVE pain [60] and is advantageous for the lack of necessity for repeated administration. Recent data also showed that LNG-IUS was a safe and viable technique to alleviate pain, improve sexual function and quality of life when given after transvaginal partial excision of rectovaginal endometriosis [66].

LNG-IUS was also evaluated for preventing post-operative endometrioma recurrence, however it did not show any benefit at 30 months follow-up. The rate of dysmenorrhea and number of endometrioma requiring further surgical or hormone treatment were significantly lower compared to controls [67]. However, it is effective to prevent recurrence if inserted after six cycles of GnRH analouge treatment to 7% [68]. The preventive ability of LNG-IUS towards post-operative recurrence of endometrioma was also assessed against cyclic oral contraceptives, which was found to be comparable [69] and against estradiol valerate with DNG, it was also found to be non-significant [70].

LNG-IUS should be the choice for those looking for a non-patient dependent and long term treatment for endometriosis associated pain.

Amongst the progestins, NETA (norethindrone) and DMPA are available and approved by the USFDA for endometriosis. Other progestins that are available but not licensed for endometriosis in the U.S. are oral MPA and Mirena, while DNG is only available in combination with estrogen. Marketing for Dydrogesterone and Etonogestrel has been discontinued, while CPA is not available.

## Conclusions

Medical management is still an attractive option for the management of endometriosis as it avoids surgical complications, especially preservation of ovarian function. Hormonal therapy remains the mainstay of medical treatment. An ideal hormonal therapy for endometriosis should be able to reduce the ectopic size, ameliorate pain, avoid hypo-estrogenic state and restore fertility with limited side effects, suitable for long-term administration and cost effective. Progesterone resistance is touted as one of the important cause of endometriosis. Thus, manipulation of PRs by medical therapy for improvement of endometriosis symptoms has shown to be effective. Progestins are an effective form of medical treatment with a variety of derivatives with multiple routes of administration. All of which, carries progestagenic effects and its benefits towards endometriotic lesion and its associated symptoms. Recent evidence of variable quality clinical studies has shown and confirms most benefits that were already known with new concerns regarding its effects on BMD in the adolescent group.

## Disclosure statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

## Funding

This mini-review is in support of the molecular research being done on PR isoforms in endometriosis, which has received ethical approval and funding from our center: FFF-2017–045; and FRGS/1/2017/SKK08/UKM/01/4. This study was also supported by Fundamental Grant UKMMC and Fundamental Research Grant Malaysia.

## References

[1] Vercellini P, Somigliana E, Viganò P, et al. Endometriosis: current therapies and new pharmacological developments. Drugs 2009;69:649–675.

[2] Pankratjevaite L, Samiatina-Morkuniene D. A case report of thoracic endometriosis – a rare cause of haemothorax. Int J Surg Case Rep. 2017;33:139–142.

[3] Angioni S, Cofelice V, Sedda F, et al. Progestins for symptomatic endometriosis: results of clinical studies. Curr Drug Ther. 2015;10:91–104.

[4] Jones CJP, Inuwa IM, Nardo LG, et al. Eutopic endometrium from women with endometriosis shows altered ultrastructure and glycosylation compared to that from healthy controls—a pilot observational study. Reprod Sci. 2009;16:559–572.

[5] Locci R, Nisolle M, Angioni S, et al. Expression of the gamma 2 chain of laminin-332 in eutopic and ectopic endometrium of patients with endometriosis. Reprod Biol Endocrinol. 2013;11:94.

[6] Kitawaki J, Kado N, Ishihara H, et al. Endometriosis: the pathophysiology as an estrogen-dependent disease. J Steroid Biochem Mol Biol. 2002;83:149–155.

[7] Zeitoun K. Deficient 17beta-hydroxysteroid dehydrogenase type 2 expression in endometriosis: failure to metabolize 17beta-estradiol. J Clin Endocrinol Metabol. 1998;83:4474–4480.

[8] Noble LS. Prostaglandin E2 Stimulates Aromatase Expression in Endometriosis-Derived Stromal Cells*. J Clin Endocrinol Metabol. 1997;82:600–606.

[9] Fu J, Song H, Zhou M, et al. Progesterone receptor modulators for endometriosis. Cochrane Database Syst Rev. 2017;7:CD009881.

[10] Wu L, Einstein M, Geissler WM, et al. Expression cloning and characterization of human 17 beta-hydroxysteroid dehydrogenase type 2, a microsomal enzyme possessing 20 alpha-hydroxysteroid dehydrogenase activity. J Biol Chem. 1993;268:12964–12969.

[11] Rousseau-Merck MF, Misrahi M, Loosfelt H, et al. Localization of the human progesterone receptor gene to chromosome 11q22–q23. Hum Genet. 1987;77:280–282.

[12] Kastner P, Krust A, Turcotte B, et al. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. EMBO J. 1990;9:1603.

[13] Horwitz KB, Alexander PS. In situ photolinked nuclear progesterone receptors of human breast cancer cells: subunit molecular weights after transformation and translocation. Endocrinology 1983;113:2195–2201.

[14] Alexander IE, Clarke CL, Shine J, et al. Progestin Inhibition of Progesterone Receptor Gene Expression in Human these steroids is determined in part by the cellular Breast Cancer Cells. Mol Endocrinol. 1989;3:1377–1386.

[15] Lessey BA, Sue Alexander P, Horwitz KB. The subunit structure of human breast cancer progesterone receptors: characterization by chromatography and photoaffinity labeling. Endocrinology 1983;112:1267–1274.

[16] Conneely OM, Sullivan WP, Toft DO, et al. Molecular cloning of the chicken progesterone receptor. Science 1986;233:767–771.

[17] Giangrande PH, McDonnell DP. The A and B isoforms of the human progesterone receptor: two functionally different transcription factors encoded by a single gene. Recent Prog Hormone Res. 1998;54:291–313.

[18] Attia GR. Progesterone receptor isoform A but not B is expressed in endometriosis 1. J Clin Endocrinol Metabol. 2000;85:2897–2902.
[19] Bulun SE. Endometriosis. N Engl J Med. 2009;360:268–279.
[20] Reis FM, Petraglia F, Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. Hum Reprod Update. 2013;19:406–418.
[21] Han SJ, O'Malley BW. The dynamics of nuclear receptors and nuclear receptor coregulators in the pathogenesis of endometriosis. Hum Reprod Update. 2014;20:467.
[22] Joshi NR, et al. Progesterone resistance in endometriosis is modulated by the altered expression of MicroRNA-29c and FKBP4. J Clin Endocrinol Metabol. 2017;102:141–149.
[23] Vercellini P, Pietropaolo G, De Giorgi O, et al. Treatment of symptomatic rectovaginal endometriosis with an estrogen–progestogen combination versus low-dose norethindrone acetate. Fertil Steril. 2005;84:1375–1387.
[24] Bergqvist A, Theorell T. Changes in quality of life after hormonal treatment of endometriosis. Acta Obstet Gynecol Scand. 2001;80: 628–637.
[25] Morotti M, Venturini PL, Biscaldi E, et al. Efficacy and acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis. Eur J Obstetr Gynecol Reprod Biol. 2017;213:4–10.
[26] Taniguchi F, Enatsu A, Ikebuchi A, et al. Efficacy of norethisterone in patients with ovarian endometrioma. Yonago Acta Med. 2017;60:182–185.
[27] Lee D-Y, Lee J-Y, Seo J-W, et al. Gonadotropin-releasing hormone agonist with add-back treatment is as effective and tolerable as dienogest in preventing pain recurrence after laparoscopic surgery for endometriosis. Arch Gynecol Obstet. 2016;294:1257–1263.
[28] Harrison RF, Barry-Kinsella C. Efficacy of medroxyprogesterone treatment in infertile women with endometriosis: a prospective, randomized, placebo-controlled study. Fertil Steril. 2000;74:24–30.
[29] Tsai H-W, Wang P-H, Huang B-S, et al. Low-dose add-back therapy during postoperative GnRH agonist treatment. Taiwanese J Obstetr Gynecol. 2016;55:55–59.
[30] Vercellini P, De Giorgi O, Mosconi P, et al. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. Fertil Steril. 2002;77:52–61.
[31] Hayashi A, Tanabe A, Kawabe S, et al. Dienogest increases the progesterone receptor isoform B/A ratio in patients with ovarian endometriosis. J Ovarian Res. 2012;5:31.
[32] Harada T, Momoeda M, Taketani Y, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis—a randomized, double-blind, multicenter, controlled trial. Fertil Steril. 2009;91:675–681.
[33] Köhler G, Faustmann TA, Gerlinger C, et al. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of dienogest daily for endometriosis. Int J Gynecol Obstetr. 2010;108:21–25.
[34] Strowitzki T, Faustmann T, Gerlinger C, et al. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstetr Gynecol Reprod Biol. 2010;151:193–198.
[35] Strowitzki T, Marr J, Gerlinger C, et al. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. Hum Reprod. 2010;25:633–641.
[36] Strowitzki T, Marr J, Gerlinger C, et al. Detailed analysis of a randomized, multicenter, comparative trial of dienogest versus leuprolide acetate in endometriosis. Int J Gynecol Obstetr. 2012;117: 228–233.
[37] Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2012;285:167–173.
[38] Maiorana A, et al. Efficacy of dienogest in improving pain in women with endometriosis: a 12-month single-center experience. Arch Gynecol Obstet. 2017;296:429–433.
[39] Lang J, et al. Dienogest for treatment of endometriosis in chinese women: a placebo-controlled, randomized, double-blind phase 3 study. J Women's Health. 2018;27:148–155.
[40] Momoeda M, Taketani Y, Terakawa N, et al. A randomized, double-blind, multicenter, parallel, dose-response study of dienogest in patients with endometriosis. Jpn Pharmacol Therapeut. 2007;35:769.
[41] Harada M, Osuga Y, Izumi G, et al. Dienogest, a new conservative strategy for extragenital endometriosis: a pilot study. Gynecol Endocrinol. 2011;27:717–720.
[42] Leonardo-Pinto JP, Benetti-Pinto CL, Cursino K, et al. Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission. Eur J Obstetr Gynecol Reprod Biol. 2017;211:108–111.
[43] Yamanaka A, Hada T, Matsumoto T, et al. Effect of dienogest on pain and ovarian endometrioma occurrence after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis. Eur J Obstetr Gynecol Reprod Biol. 2017;216:51–55.
[44] Seo J-W, Lee D-Y, Yoon B-K, et al. Effects of long-term postoperative dienogest use for treatment of endometriosis on bone mineral density. Eur J Obstetr Gynecol Reprod Biol. 2017;212:9–12.
[45] Ebert AD, Dong L, Merz M, et al. Dienogest 2 mg daily in the treatment of adolescents with clinically suspected endometriosis: the VISanne study to assess safety in ADOlescents. J Pediatr Adolesc Gynecol. 2017;30:560–567.
[46] Rižner TL, Brožič P, Doucette C, et al. Selectivity and potency of the retroprogesterone dydrogesterone in vitro. Steroids 2011;76: 607–615.
[47] Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. Maturitas 2003;46:7–16.
[48] Tumasian KP, Bespoiasnaia VV, Voronovskaia IV. Treatment of endometriosis in female infertility. Likars' Ka Sprava/Ministerstvo Okhorony Zdorov'ia Ukrainy. 2000;3:103–105.
[49] Overton CE, Lindsay PC, Johal B, et al. A randomized, double-blind, placebo-controlled study of luteal phase dydrogesterone (Duphaston) in women with minimal to mild endometriosist. Fertil Steril. 1994;62:701–707.
[50] Trivedi P, Selvaraj K, Mahapatra PD, et al. Effective post-laparoscopic treatment of endometriosis with dydrogesterone. Gynecol Endocrinol. 2007;23:73–76.
[51] Zou S, et al. Oral continuous combined 0.5 mg estradiol valerate and 5 mg dydrogesterone as daily add-back therapy during post-operative GnRH agonist treatment for endometriosis in Chinese women. Int J Clin Exp Med. 2013;6:67–73.
[52] Crosignani PG, Luciano A, Ray A, et al. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod. 2006;21:248–256.
[53] Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol. 1996;175:396–401.
[54] Carr B, Dmowski WP, O'Brien C, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. Reprod Sci. 2014;21:1341–1351.
[55] Cheewadhanaraks S. Cumulative recurrence rates of endometriosis-associated pain after long-term intramuscular depot medroxyprogesterone acetate therapy. J Med Assoc Thai. 2013;96:140–143.
[56] Walch K, Unfried G, Huber J, et al. Implanon® versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis—a pilot study. Contraception 2009;79:29–34.
[57] Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon®. Contraception 1998;58:99S–107S.
[58] Beerthuizen R, van Beek A, Massai R, et al. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon® compared to a non-hormonal method of contraception. Hum Reprod. 2000;15:118–122.
[59] Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, et al. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. Obstet Gynecol. 2012;119:519–526.
[60] Vercellini P, Viganò P, Somigliana E. The role of the levonorgestrel-releasing intrauterine device in the management of symptomatic endometriosis. Curr Opin Obstetr Gynecol. 2005;17:359–365.
[61] Lockhat FB, Emembolu JO, Konje JC. The evaluation of the effectiveness of an intrauterine-administered progestogen (levonorgestrel) in the symptomatic treatment of endometriosis and in the staging of the disease. Hum Reprod. 2004;19:179–184.
[62] Matorras R, et al. Efficacy of the levonorgestrel-releasing intrauterine device in the treatment of recurrent pelvic pain in multitreated endometriosis. J Reprod Med. 2010;56:497–503.
[63] Lockhat FB, Emembolu JO, Konje JC. The efficacy, side-effects and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen (levonorgestrel): a 3 year follow-up. Hum Reprod. 2005;20: 789–793.

[64] Bayoglu Tekin Y, Dilbaz B, Altinbas SK, et al. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril. 2011;95:492–496.
[65] de Sá Rosa e Silva ACJ, Rosa e Silva JC, Nogueira AA, et al. The levonorgestrel-releasing intrauterine device reduces CA-125 serum levels in patients with endometriosis. Fertil Steril. 2006;86:742–744.
[66] Li T, et al. Efficacy and impact on quality of life of different drug treatments after partial resection of rectovaginal endometriosis. Zhonghua Fu Chan Ke Za Zhi. 2017;52:307.
[67] Chen Y-J, et al. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. Am J Obstetr Gynecol. 2017;216:582.e1–582.e9.
[68] Kim MK, Chon SJ, Lee JH, et al. Postoperative levonorgestrel-releasing intrauterine system insertion after gonadotropin-releasing hormone agonist treatment for preventing endometriotic cyst recurrence: a prospective observational study. Reprod Sci. 2018;25:39–43.
[69] Cho S, Jung JA, Lee Y, et al. Postoperative levonorgestrel-releasing intrauterine system versus oral contraceptives after gonadotropin-releasing hormone agonist treatment for preventing endometrioma recurrence. Acta Obstet Gynecol Scand. 2014;93:38–44.
[70] Morelli M, Sacchinelli A, Venturella R, et al. Postoperative administration of dienogest plus estradiol valerate versus levonorgestrel-releasing intrauterine device for prevention of pain relapse and disease recurrence in endometriosis patients. J Obstet Gynaecol Res. 2013;39:985–990.