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Current Controversies and Future Directions for Endometriosis Therapy

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INTRODUCTION

Endometriosis (Em) by definition is the presence of endometrial like tissue outside the uterus which is associated with a chronic inflammatory reaction. Cellular proliferation, invasion and angiogenesis are important features which help in establishing along with progression and recurrence of disease. Also sloughing of the oestrogen dependent endometrial tissues => chronic inflammatory processes mediated by excessive production of cytokines and prostaglandins. This inflammation along with subsequent adhesions and scarring are what => patients symptoms of pain and other morbidities like infertility [1].

In our previous review on pathophysiology and management we discussed use of OCP's, progestins, danazol, GnRH agonists aromatase inhibitors and PPARγ inhibitors like pioglitazone along with telmisartan having PPARγ partial agonism along with angiotensin II agonistic activity, immunomodulators like rapamycin, lipoxin 4, and pentoxifylline, Oral Gn RH antagonists like egalogolix [2].

Despite decades of research pathophysiology of Em remains ill understood and treatment remains suppressive rather than curative.

Advantages of Pg over OCP's

Here we try to emphasize the disadvantages of using oral contraceptives as first lines of treatment and instead use of progesterone alone medications as first line therapy and how no definite biomarker is available as reviewed recently by Ahn., *et al*. 2017 and how micro RNA's or long coding RNAs may be better than previously used cytokines like cancer antigen(CA)125/CA19-9 [3].

Further with our deeper understanding of control of Gn RH neurons by KNDy neurons by kisspeptin/neurokinin B/dynorphin {KNDy} neurons, how further research can be directed in that area is discussed.

At present therapy for symptomatic Em are based on patients choices, goals of treatment, adverse effects, efficacy, cost, associated co-morbidities and availability [4].

Contrary to the earlier belief that OCP are the first line of treatment for menstrual and pelvic pain associated with Em and as per the guidelines of ACOG, ASRM, ESHRE, Canadian Fertility and Andrology Societies (CFAS) Casper R2017 reviewed how there is no evidence for efficacy of the same [5]. There is biological data and though scarce data exists regarding that there are potential adverse effect of long term use of OCP's on the progression of Em for treatment of pelvic pain associated with Em. Opposite to that, there is a

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randomized controlled data which supports the use of oral progesterone (Pg) only treatment for pelvic pain associated with Em and for supporting the anatomic extent of endometriotic lesions. Norethindrone acetate (NETA) along with medroxy progesterone acetate (MPA) and dienogest a 4th generation steroidal progesterone has regulatory approval for treating Em and thus maybe better than OCP's for first line therapy [5].

Reason given for OCP's being ineffective in activities of endometriotic implants is suggested by reports of Bulun., *et al* [6,7]. In eutopic endometrium oestrogen in follicular phase acts via estrogen receptors (ER) to increase transcription and protein levels of the PR especially the PRB isoform [8]. In the luteal phase Pg acts via PRB to down-regulate ER and increase the transcription and secretion of the enzyme 17β hydroxyl steroid dehydrogenase type 2 (HSD17β2) [7], which catalyzes the conversion of E2 to less active estrone. This effect is transcriptionally regulated by downstream PRB signaling which involves retinoic acid and Sp1/Sp3 dependent pathway [9]. In Em implants ERα is decreased but ERβ is upregulated [10,11] => complete loss of PR B [12] and the inability to induce HSD17β2 [7] within implants, hence show resistance to Pg and have increased Og activity.

Low dose OCP's contain 20 - 30 μg of EE. Basic research [13] and data from clinical menopausal hormone therapy [10] suggest that 5 μg of EE is equivalent to 1mg micronized E2 or 0.625 mg of conjugated equine estrogen. Therefore, the dose of EE in a low dose OCP is equivalent to 4 – 6 times the physiologic dose of Og. The OCP also contains a progestin designed to antagonize the Og effects on the Endometrium. It is possible that giving high doses of Og and Pg in an OCP based on ER and PR alteration is counterproductive => Og dominance in the presence of Pg resistance. Based on earlier work by DIzerrega [14] and Vercelini [15] suggested that the presence of supraphysiologic concentration of Og with the OCP during what should be the menstrual phase may rescue endometrial cell clusters deposited in the pelvis during retrograde menses.

Further Vercelini [15] showed decreased risk of Em in current user of OCP's but increase in Em risk in past users of OCP's. Chapron [16] also showed an increased incidence of Em in the past users of OCP's. They also found an increased incidence of deep infiltrating Em in women who had taken OCP's in past which suggests that ultimate failure of OCP to relieve pain but also that lower dose of Og in OCP's could => progression of disease to make an invasive type.

Why Pg should be effective in Pg alone therapy in mg/day doses is that it inhibits ovulation [17,18] and induces amenorrhea which should prevent dysmenorrhea. The decrease in gonadotropin secretion induced centrally by the action of potent Pg's will result in a relatively hypoestrogenic state which could help in suppressing Em and definitely in progression of disease. Mostly these treatment help in retaining some Og activity to spare bone density [19]. Also, Pg's have an anti-inflammatory and antiangiogenic activity [20-23]. Also, Pg may reduce matrix metalloproteinases and hence decrease invasiveness [24].

NETA in 2.5 - 5 mg dose daily [18], MPA in early studies unlike OCP's completely finished the pelvic pain and dysmenorrhea in women with Em and reduced the implant size on 2nd look laparoscopy [17] or decreased endometrioma size on USG [18]. Similarly, dienogest a 19 nortestosterone derivative has received regulatory approval for Em in Europe and Canada [25]. NETA is less expensive and dienogest is slightly better tolerated because of lower side effects [25] hence choice depends on patients affordability and preference. Furthermore, role of dienogest and GnRH agonist in long term Em is reviewed in reference number [26].

Future Directions

Recent work in neuroendocrinology, endocrinology, tumorigenesis, neurogenesis and genomic will markedly change the approaches used for current management approaches.

Important recent findings are

1. In arcuate nucleus, there are neurons colocalized which comprise of three neuropeptides namely kisspeptins (kp), neurokinin B (NKB), dynorphin, which are collectively known as KNDy neurons. They interact to influence the GnRH release, where kp stimulates, NKB modulates and dynorphin inhibits the

pulsatile GnRH s release [27]. Thus, KNDy hypothesis gives suggestion that KNDy neurons in Arc nucleus may interact to control the pulsatility of GnRH [28,29]. For the first time in humans LH was used as a surrogate marker to demonstrate the interaction of KNDy signaling regulating GnRH release and pulsatility [30]. Bedaiwy., *et al*. showed that kp is differentially expressed at the level of endometriosis in patients with and without Em. Additionally, kp expression was statistically significantly lower in deep infiltrating endometriomas, as compared to superficial peritoneal disease [31]. This has important implications not only for improving our understanding of the pathogenesis of Em but also for optimizing novel hormonal agents to treat different disease phenotype and explains how GnRH agonists may act.

2. Em as a major cause of chronic pelvic pain(CPP) acts as a cyclic source of peripheral nociceptive input. Current data support the hypothesis that changes in central pain system also plays an important role in the development of chronic pain regardless of the process of Em. Women with Em associated CPP showed decreased gray matter volume in brain regions involved in pain perception. Women with CPP without Em also showed decrease in gray matter. These changes were not seen in pts with Em who had no CPP [32]. Hence one has to take into consideration the presence or absence of CPP, when talking about CPP. In the Em patients with central sensitization other treatment strategies could be suggested like neuromodulators or myofacial trigger point injections, one can consider approaches targeting multidisciplinary factors to the sensitized patients like physiotherapy [33], along with cognitive therapy [34] although greater number of trials are needed.

3. Em has been associated with local neurogenesis which in combination with central sensitization would further amplify pain signaling with use of highly phenotyped patients having cul-de-sac /uterosacral Em with or without deep dyspareunia. The group of Bedaiwy., *et al*. found that the local nerve bundle density was statistically significantly higher in women with deep dyspareunia [35]. Nerve growth factor has been shown to be a major neurotrophic factor in Em [36] and maybe implicated in this increase in local nerve density. Further research into the signaling underlying neurogenesis in Em is needed to identify potential treatment targets.

4. Treatment targeted to genes associated with Em research remain a future hope. Genome wide association studies have demonstrated various reproducible loci associated with Em especially in moderate to severe disease [37]. Before one can translate these findings to clinical practice greater work is required to identify genes adjacent to the loci with aetiopathologic importance in Em and the signaling pathway associated with these genes.

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