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Review

Pathophysiological Basis of Endometriosis-Linked Stress Associated with Pain and Infertility: A Conceptual Review

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Abstract: Women with endometriosis are often under stress due to the associated pain, infertility, inflammation-related and other comorbidities including cancer. Additionally, these women are also under stress due to taboos, myths, inter-personal troubles surrounding infertility and pain of the disease as well as due to frequent incidences of missed diagnosis and treatment recurrence. Often these women suffer from frustration and loss of valuable time in the prime phase of life. All these complexities integral to endometriosis posit a hyperstructure of integrative stress physiology with overt differentials in effective allostatic state in women with disease compared with disease-free women. In the present review, we aim to critically examine various aspects of pathophysiological basis of stress surrounding endometriosis with special emphasis on pain and subfertility that are known to affect the overall health and quality of life of women with the disease and promising pathophysiological basis for its effective management.

Keywords: allostasis; comorbidity; endometriosis; infertility; inflammation; pain

1. Introduction

Endometriosis occurs due to the growth of endometrium-like tissue outside the uterus. As summarized in Figure 1, it is a complex disorder that is influenced by genetic, epigenetic and environmental factors [1–5]. Endometrial cells, stem cells and bone marrow cells with genetic and epigenetic defects after implantation and metaplasia within an abnormal environment of the peritoneal cavity progress to form the typical ectopic lesions in ovary, peritoneum and rectovaginal compartments [6,7]. Endometriosis is associated with chronic inflammatory disorder state along with pelvic pain affecting 10–15% women during their reproductive years, as well as with primary infertility in 50% women [8–10].

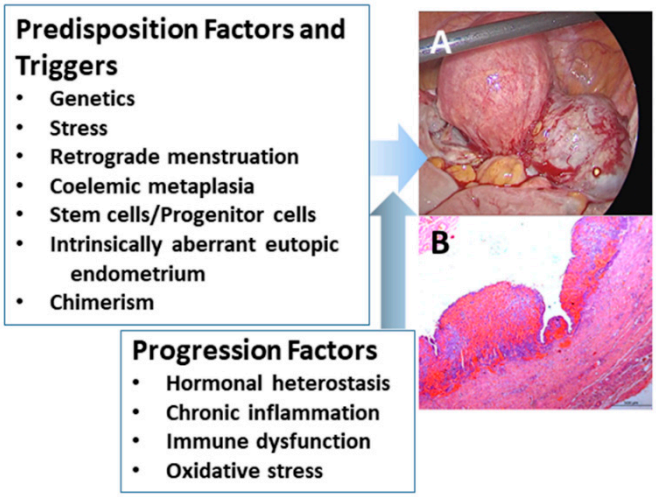

Figure 1. A simplified schema of histogenesis of endometriosis involving several predisposing, triggering and progression factors. It is notable that dysregulated allostatic load at the local and systemic levels plays critical role in the inducement of ectopic lesions of endometriosis. Adapted from Ghosh et al. [11]. (**A**) Laparoscopic view of right ovarian endometrioma with severe adhesion obliterating the pouch of Douglas. (**B**) Low magnification histopathological features of an ovarian endometriotic cyst with circumscribed stromal nodule and epithelial lining seen (**B**).

Endometriosis impairs the quality of life due to chronic and severe acyclic pelvic pain with associated dysmenorrhea, dyspareunia, gastrointestinal problems, fatigue and headaches [12,13]. Beside pelvic pain, endometriosis is associated with subfertility. The fecundity rate for a couple with the woman partner having endometriosis is reduced to 2–10%, as compared to 15–20% among endometriosis-free controls [14]. This is true for the Caucasian population, and more so for Asian women [15,16].

Stress from endometriosis-associated pain and infertility, although well perceived, appears enigmatic due to underlying multifactorial complexities. Women with endometriosis often suffer from several inflammation-linked and other comorbidities (see Figure 2 for details).

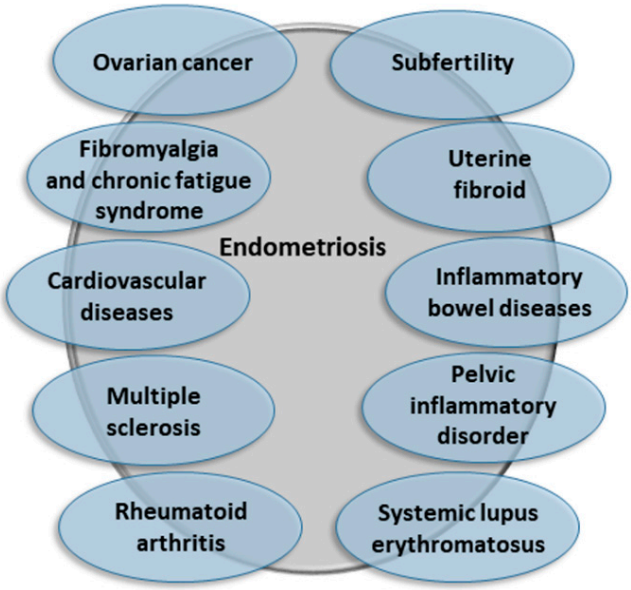

Figure 2. The comorbidities associated with endometriosis. The incidence of developing several comorbidities was significantly higher among women with endometriosis as compared to women without endometriosis. For details, see references [17–21].

As a result, women with endometriosis are often surrounded by taboos, myths, scourge of subfertility, pain of disease and missed diagnosis and treatment [22]. Delays in the diagnosis and initiation of treatment for the disease in fact occur due to these counterproductive factors operative both at the individual patient level and at the medical level resulting in frustration and loss of valuable time in the prime phase of life of the patient [22–25]. While endometriosis is generally considered to be benign, the moderate probability that endometriosis may be associated with incidences of ovarian and extra-ovarian cancers adds to the mounting stress on the women affected by the disease [6,11]. A dramatic image hoisted by the World Endometriosis Research Foundation attempts to encapsulate the stress of endometriosis that affects an estimated 200 million women worldwide (see Figure 3). In the present narrative review, we aim to examine various aspects of stress physiology during endometriosis with special emphasis on pain and infertility that can affect the overall health and quality of life of women with the disease. At the end, a brief discussion on the future course of targeted research to strategize for its management will be addressed.

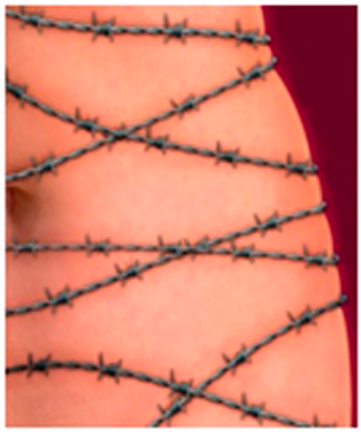

Figure 3. A symbolic image of women with endometriosis entrapped not only by organic inflictions in form of pain, subfertility and various comorbidities including cancer but also scourges of taboos, myths, stigmatization, missed diagnosis and treatment, frustration and loss of valuable time in the prime phase of the life of an estimated 200 million women worldwide. This image has been reproduced with the permission of the World Endometriosis Research Foundation.

2. Methods

To meet the objectives as indicated above, we drew upon in this review a method of concept-centric interpretive process incorporating a diverse set of quantitative and qualitative questions and studies from a range of disciplines. Thus, we employed a method of critical narrative synthesis process, not a classic systematic review methodology [26–28]. However, we adhered to the PRISMA principles as far as applicable for this type of review [29,30]. A primary computerized search for relevant peer-reviewed publications available in English language was systematically conducted based on key word terms retrieved from MeSH browser and using three databases (PubMed, MEDLINE and EMBASE) and Google Scholar. The MeSH key word terms used were endometriosis AND allostasis OR comorbidity OR infertility OR inflammation OR pain OR stress OR social impact OR psychological impact AND humans. Two authors (DG and JS) independently screened the titles and abstracts and identified relevant papers for which full texts were available. Additional relevant articles referred in the bibliographies of the retrieved articles and reviews and perceived to be significant for the present study were then searched and retrieved. Anecdotal reports, editorials, letters to the editor, conference abstracts, duplicate papers, reviews without any originality, hypothesis papers, reports of surgical technique and trials, surgical and diagnostic case reports were not included. The specific inclusion criteria for the present review included publications that unambiguously provided visual and/or histological confirmation of endometriosis, defined as the presence of peritoneal endometriotic

lesions, and/or ovarian endometriotic lesions (or endometrioma), and/or deep infiltrating endometriosis (or rectovaginal nodules), and publications in which patients had clearly shown to have, and controls had not had endometriosis confirmed by surgical verification. Specific attention was given to reduce any strong bias in administrating selection criteria for questions and articles [31].

3. A Brief Overview on How Endometriosis Affects Women's Health and Beyond

Endometriosis is often seen in women with infertility and pelvic pain: up to 5 in 10 women with infertility suffer from endometriosis, and 7 out of 10 women with endometriosis suffer from chronic pelvic pain [32,33], yet the disease may remain asymptomatic. While the prevalence of asymptomatic endometriosis is not clearly known, up to 45% of women undergoing laparoscopic sterilization have been diagnosed with endometriosis [34]. Additionally, women and their family and friends are often unaware of endometriosis as a debilitating condition that requires medical attention. Often, the symptoms of endometriosis are casually perceived as part of "normal" menstrual irregularities, and menstrual pain is considered integral to womanhood and so to be "endured" [35]. Women may also be reluctant to disclose menstrual irregularities and pain, which may be associated with endometriosis due to the practices of "menstrual etiquette", and its disclosure may be considered as a "discrediting attribute" resulting in stigmatization. Such perceptions together with the societal stigma that upend any discussion of such problems may contribute to delays that often span 5–7 years in seeking medical help for endometriosis and its diagnosis [36]. Delays also occur at the medical level due to the delay in referral from primary to secondary care, pain normalized by clinicians, intermittent hormonal suppression of symptoms, use of non-discriminating investigations and insufficiency in awareness and lack of constructive support among a subset of healthcare providers [23–25,37,38]. In this connection, it is noteworthy that delay in diagnosis is longer for women reporting with pelvic pain compared with those reporting with infertility, which is suggestive of the fact that there is a higher level of reluctance surrounding endometriosis-associated pain symptoms [38–40]. Additionally, many clinicians admittedly are not sufficiently trained to provide necessary care to the patients regarding the psychosocial aspects of the disease [25,37,41]. Furthermore, the disease strongly affects the social activities, working efficiencies, interpersonal and sexual life and self-esteem especially in patients experiencing pain symptoms [42]. Although several studies indicated that long-term pharmacological treatment for endometriosis offers symptomatologic relief up to 70% of women suffering from pelvic pain (for details see later under "Physiological Basis of Management of Endometriosis-Associated Medical Problems" section), there exists very little curative treatments to provide sufficient relief from endometriosis, and surgical treatments most often result in high rates of recurrence [43], which adversely affect patient's psychosocial wellbeing and quality of life with an associated relative increase in the total healthcare spending due to the presence of comorbidities [24,38,44]. Additionally, the risk of gynecological cancers in susceptible and vulnerable population of patients with endometriosis is not negligible [11,45,46].

4. Different Facets of Endometriosis-Associated Stress

Hans Selye had defined stress as set of "non-specific responses that can be resulted from a variety of different kinds of stimuli" [47]. While Selye's stress theory focused primarily on physiological stress, psychological factors also play a significant role in the occurrence of physiological and psychological stress responses. Stress occurs to individuals who "perceive" that their coping capacity is not on a par with the demands that they face from the external world [48]. According to the "transactional model of stress", stress is considered as a product of the interaction between the individual and the environment. Thus, stress is a state in which several extrinsic and intrinsic disturbances as "stressors" are perceived to threaten homeostasis. Stress may trigger activation of neural, neuroendocrine and immune mechanisms towards achieving "stability through change", referred to as "allostasis" [49]. Genetic, developmental and socio-economic factors as well as cultural background and natural developmental history including exposure to stressors and protective factors determine the baseline allostatic state of physiological

regulation in a given individual [50]. Contextual and habitual processes influence the psychological and physiological responses to acute and daily stressors. The entropy of "unexpected surprise" or an "uncertainty" due to stress may create a critical constraint tapping on cerebral energy, which when dysregulated leads to allostatic load and ultimately affects health behaviors leading to diseases [51].

The diagnosis of endometriosis *per se* is considered to be a perceived stress associated with the neuroendocrine disequilibrium that contributes to disease progression [17]. As discussed above, endometriosis afflicts several spheres in a woman's life, namely, physical, psychological, emotional, marital, sexual and professional to create a strong negative impact on women's subjective wellbeing [52]. While determining the degree of correlations between stress, depression levels and the coping strategies that can be provided to patients with endometriosis, Donatti et al. observed that the stress levels (alert/resistance or exhaustion/almost exhaustion) and the type of stress (physical, psychological or both) were significantly correlated with chronic acyclic pelvic pain, depression and the stage of endometriosis (minimal to mild versus moderate to severe) [53]. In these groups of patients suffering from endometriosis, such coping strategies have shown a positive association between coping, depression levels, type and levels of stress and the intensity of pain being experienced. In a systematic review, it was concluded that women presenting with endometriosis were at risk from psychosocial disturbances or psychiatric distress and should therefore be screened for psychosocial and psychiatric disturbances [13]. However, the question whether such disruptions are a consequence of endometriosis, due to the associated chronic gynaecological pain or other factor such as inflammation requires further investigations.

A reduced quality of life, high levels of perceived stress and anxiety and depressive symptoms are found to be often present in patients experiencing endometriosis than those reported by patients with other chronic inflammatory disorders [54]. In a comparative study of quality of life and mental health, no significant difference was observed between asymptomatic endometriosis patients and the control group, while patients diagnosed with endometriosis and suffering from pelvic pain had poorer quality of life and mental health as compared to those with asymptomatic endometriosis and the healthy controls [55]. The psychoticism, introversion and anxiety scores among patients undertaking psychometric analyses prior to surgical diagnosis of endometriosis and also suffering from pelvic pain were reportedly higher as compared to the patients with pain but free of endometriosis [56]. Physiologic and neural reactivity studies document high levels of stress caused by endometriosis, and the high levels of perceived stress were reported to contribute to the progression of endometriosis [57,58]. Patients with above-threshold levels of anxiety and depression show more of infertility related-stress particularly in the inter-personal area [59]. Collectively, it appears that women with clinical manifestation of pain or infertility or both along with diagnosed endometriosis are significantly susceptible to experience high degree of stress. Figure 4 provides a tentative *modus operandi* to entail how endometriosis-linked stress may affect the top-down neuroendocrine regulation resulting in stress related pathophysiology in women with the disease. The fact that there exists a functional dialogue between neuronal and inflammatory mediators poses a critical wedge in this process [60–62].

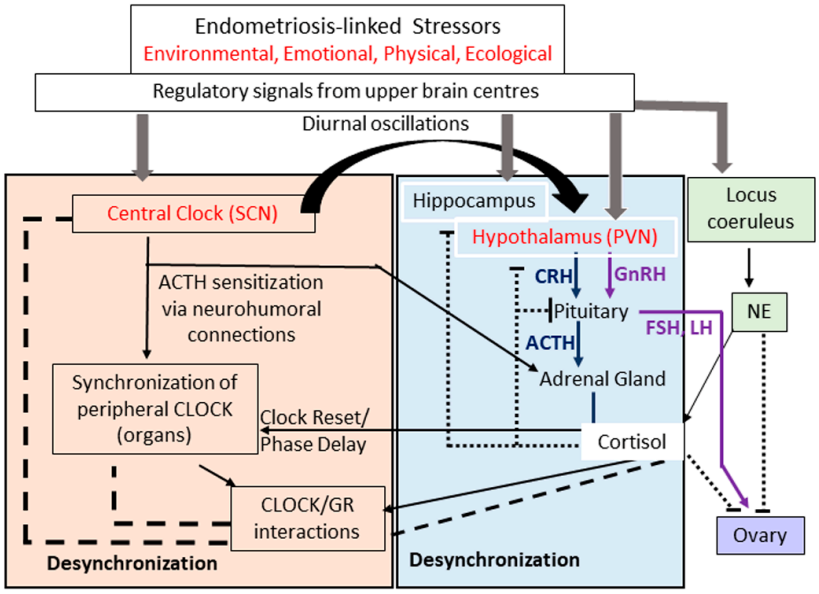

Figure 4. Top-down regulation of reproductive physiology by environmental, ecological, emotional and physical stressors in women with endometriosis. Neurons in limbic system and cortex respond to stressors (acute/chronic) to regulate reproductive behavior and reproductive functions via the hypothalamic-pituitary-adrenocortical (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis with the involvement of the circadian system via suprachiasmatic nucleus (SCN). The HPA axis activated in response to stress initiates hypothalamic release of corticotropin-releasing hormone (CRH) that stimulates secretion of adrenocorticotropic hormone (ACTH) from pituitary, increases cortisol production and secretion from adrenal cortex with concomitant inhibition of the HPG axis and reproduction. Acute and chronic stress via locus coeruleus and paraventricular nucleus (PVN) operates to release corticotropin releasing hormone (CRH) and arginine vasopressin (AVP), which via the release of ACTH from pituitary promote adrenal gland cortisol secretion. Acute/chronic stress inhibits gonadal functions through release of norepinephrine (NE) from locus coeruleus to inhibit ovarian estrogen secretion. Increase in cortisol secretion inhibits pituitary release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and ovarian secretion of estrogen and progesterone. Stressors also exert a negative regulation of gonadotropin releasing hormone (GnRH) through modulation of CRH, gamma-amino butyric acid (GABA), kisspeptin and putative gonadotropin inhibitor hormone (GnIH) to inhibit secretion of estrogen and progesterone (not shown). Response to stressors includes feedback regulation of ACTH and GnRH acting via cortisol, estrogen, and progesterone at hypothalamic and pituitary levels. Circadian release of glucocorticoids is regulated by an interplay of the endocrine activity of the HPA axis, SCN signaling, autonomic nervous system and the actions of the peripheral adrenal clocks. Circadian-stress crosstalk under basal conditions and in response to external stressors functions with cortisol acting via its receptors (GR) at peripheral and central levels operating to maintain physiological homeostasis. Acute stress results in the release of glucocorticoids independent of the central clock-mediated circadian regulation of the HPA axis causing desynchronization and transient uncoupling of the central and peripheral clocks. Chronic stressors trigger the release of glucocorticoids by the adrenal cortex independently of the central clock-mediated diurnal regulation of HPA axis (SCN receives cortisol feedback via raphe nucleus, dorsomedial and paraventricular nuclei of hypothalamus, inflammatory cytokines and BDNF) to cause phase shifts and resetting of the peripheral clocks leading to desynchronization and uncoupling of the latter from the central clock. Desynchronizations of the circadian-adrenal clocks occur following exposure to acute and chronic stress. Acute-stress, however, may induce release of LH under relatively high estradiol levels mediated via CRH to advance the GnRH surge and ovulation. The areas shown in red colored letters are known to be influenced by inflammatory mediators. Cortisol related effectors are shown in blue color and ovarian function related effectors are shown in violet color. Source: References [62–72].

5. Pathophysiological Impact of Inflammatory Stress in Endometriosis

A growing body of evidence supports the notion that hormonal and immune factors function to activate a local inflammatory microenvironment to promote two cardinal symptoms associated with endometriosis that cause stress to the individuals with the disease: chronic pain and infertility. As seen in Figure 4, activation of stress responses takes place via the sympathetic-adreno-medullar (SAM) axis that regulates the secretion of norepinephrine and the hypothalamus-pituitary-adrenocortical (HPA) axis regulating the secretion of glucocorticoids [63,73–76]. In the presence of a sustained stressor, activation of HPA-SAM-immune axes by NF- B results in an overall increase of pro-inflammatory cytokines, which in turn decrease the anti-inflammatory cytokines contributing to the various comorbidities that are associated with endometriosis [77]. The activation of the axis is associated with high peripheral levels of corticotrophin releasing hormone (CRH), which contributes to inflammation detected in the peritoneum in case of endometriosis through an increased frequency of $CD56^{+}$-PR^{+} and $CD8^{+}$-PR^{+} peritoneal lymphocytes and higher TNF/IL10 ratio [63,78,79]. Survival, implantation and proliferation of refluxed uterine endometrial cells into the peritoneal cavity and their adherence to ectopic foci, a singular mechanism for the onset of endometriosis, is facilitated by an altered immune niche evidenced by dysfunctional peripheral $CD56^{+}$ uterine NK (uNK) cells exhibiting reduced levels of cytotoxicity in women with endometriosis [80]. The populations of T cells, B cells, dendritic cells and macrophages within the endometrium and in the ectopic lesions are generally disturbed, and the $FOXP^{+}$ regulatory T cells fail to decline in the secretory phase of menstrual cycle. These changes collectively permit proliferation, escape from apoptosis and immune surveillance of ectopic endometrial cells in endometriosis [81–83]. Moreover, interactions between macrophages and endometrial stromal cells may result in the downregulation of uNK cell cytotoxicity due to the secretion of IL10 and TGFβ, which in turn may trigger immune escape of ectopic fragments leading to the histogenesis of endometriotic lesions [84]. In Figure 5, we have proposed a schema of immune dysfunctions in the peritoneal niche involving the uterus, the peritoneal mesothelium and the ovaries surrounding an ectopic lesion in moderate to severe ovarian endometriosis. In this regard, the observed association between elevated serum concentrations of IL6 and/or IL8 and the occurrence of endometriosis-associated infertility, but not with endometriosis-associated pain, appears intriguing [85]. It may be conjectured that pelvic stress due to dysregulated cytokines manifest different functional trajectories to causing infertility *vis-à-vis* pelvic pain. In summary, it appears that pro- and anti-inflammatory cytokines, growth factors and the stress hormones prolactin and cortisol may function as participators to create a defective immune response within the peritoneal inflammatory niche and a local guidance path for the menstrual effluent cells to adhere and grow in the lesion sites to favor the development and progression of endometriosis [86].

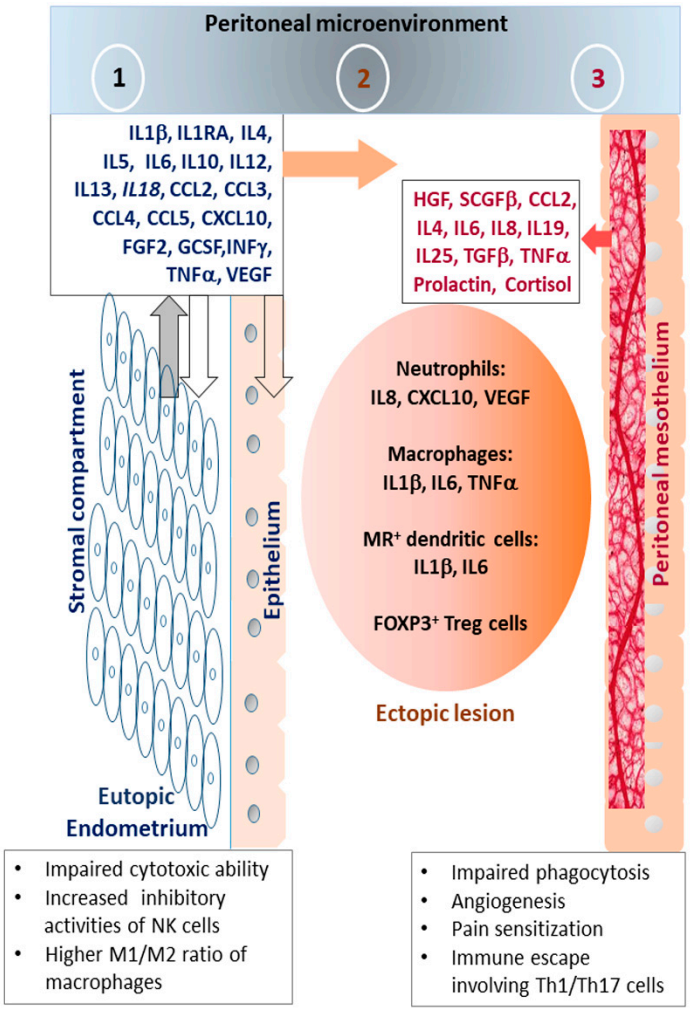

Figure 5. The molecular nature of inflammatory niche in the peritoneal microenvironment during endometriosis. A critical imbalance in inflammation-associated cytokines (shown in blue colored letters) produced by eutopic endometrial compartment (shown as 1), migratory cells and their products (shown in black colored letters) at the ectopic site of histogenesis (shown as 2) and systemic inputs (shown in red colored letters) in the peritoneal mesothelial compartment (shown as 3) forms the pathophysiological basis of microenvironmental stress in the pelvic peritoneum. Note that the concentration of IL18 (shown in italics) secretion from the mid-luteal phase eutopic endometrial stromal cells during endometriosis is lower than that from stromal cells obtained from disease-free endometrium. Source: References [58,80–82,86–101].

5.1. Endometriosis-Associated Pain

At least 70 per cent of women with non-menstrual chronic pelvic pain lasting six or more months reportedly do exhibit endometriosis [22,102]. Several studies indicate that generalized hyperalgesia and chronic pelvic pain reduce the quality of life as well as physical and mental wellbeing of individuals with endometriosis [13,55,103,104]. Although the precise mechanisms of endometriosis-associated pelvic pain remain poorly understood, its development is believed to be mediated by combined mechanisms involving nociceptive, inflammatory, and neuropathic processes [105,106]. Thus, endometriosis-associated pain may be nociceptive, inflammatory, neuropathic or a mixture of these. It is also not unlikely that endometriosis gives rise to all three types of pain, however, with one type predominating which may be determined by the developmental history of the individual and ancillary factors surrounding her [107]. Furthermore, given the widespread

locations of endometriotic lesions on both pelvic viscera and parietal peritoneum, the pain associated with endometriosis can be both visceral and somatic in origin [107].

Chronic pelvic pain is often associated with greater perception of pain along with widespread reduced pain thresholds, putatively due to central sensitization, which is associated with neurological changes in the dorsal horn of the spine, resulting in hyperactive responses to various sensory inputs and neurogenic inflammation of pelvic viscera [108,109]. The term central sensitization refers to the presence of hyperalgesia (i.e., an abnormally increased sensitivity to pain) and/or allodynia (i.e., pain from stimuli that are not normally painful) on quantitative sensory testing (QST) in animal models of nociception and is generally accompanied by enlargement of the nociceptive field and/or electrophysiological evidence of decreased firing threshold and increased discharge of spinal nociceptive neurons [110]. Thus, it refers to spinal disorder mechanisms that are responsible for augmenting nociceptive inputs in animal models [111–113]. Since the dorsal horns cannot be directly examined in the same way in the human, the widespread reduction in pain thresholds to a given stimulus are considered proxies to this phenomenon [110,114]. The results obtained from the studies performed on this paradigm indicate that endometriosis-associated chronic and persistent pelvic pain along with widespread reduced pain thresholds involves central sensitization [106,115–119].

There is substantial evidence to suggest that inflammatory mechanisms play significant role in the pathophysiology of altered central pain processing [120,121]. Cytokines produced in the inflammatory niche of endometriosis may act as mediators between the peripheral lesion and changes in the central nociceptive processes [87,122]. In fact, several of the cytokines that include CCL2, IL1, IL6, IL8, IL10, TGFB, TNFA and VEGF are known to be high in endometriosis [86,123,124], and many of these cytokines are known to mediate non-linear, multi-modal, combinatorial effects and feedforward as well as mutually positive regulation leading to a state of inflammatory over-activation and pain [107,125–128]. Administration of several of these inflammatory cytokines (IL1, IL6 and TNFA) in animal models produces both the illness responses and increased sensitivity to noxious stimuli [122,129] that could be abolished by administration of their respective and specific antagonists [129–131]. Figure 6 provides a comprehensive summary of different peripheral mechanisms putatively involved in invoking endometriosis-associated pain.

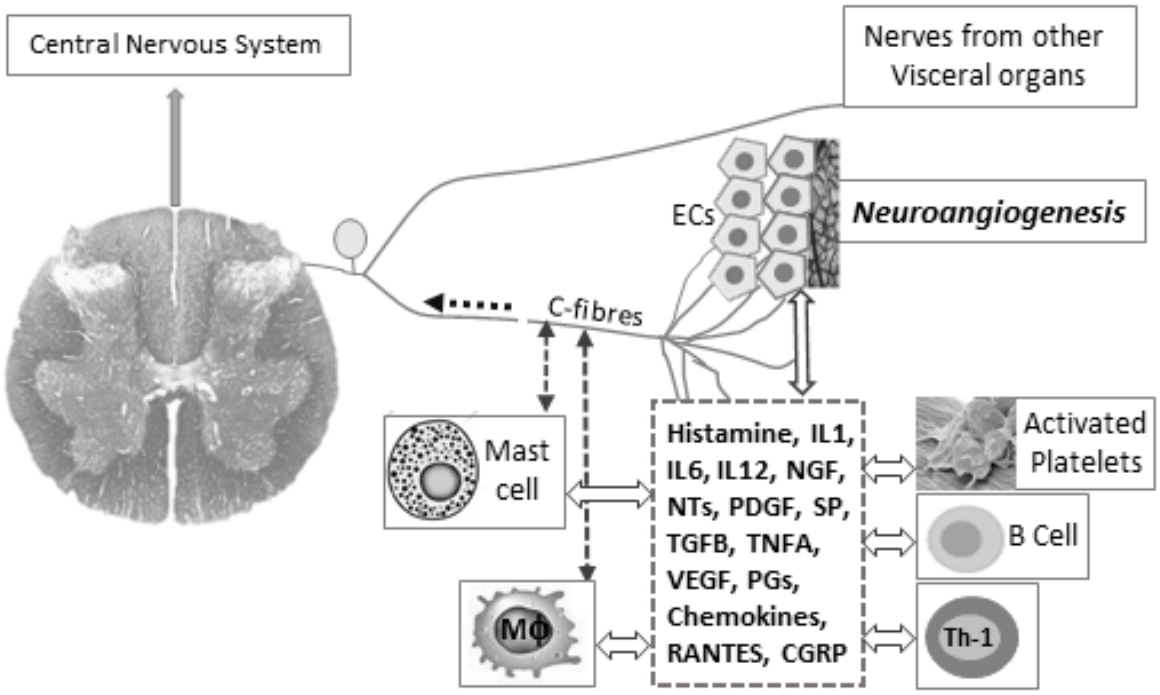

Figure 6. A summary of different peripheral mechanisms putatively involved in invoking endometriosis-associated pain. Adapted from Morotti et al. 2014 [107].

Taken together, it appears that (i) the hypersensitivity often seen in endometriosis-associated pain is causally linked to central and peripheral neural sensitization and inflammation irrespective of anatomical distortion, and (ii) conventional approaches to classifying endometriosis-associated pain based on disease, duration and anatomy are inadequate for treating endometriosis-associated pain. It is notable in this regard that location and standard scoring of endometriotic lesion depending on stage, spread and duration often fails to predict the level of pain; some women with histopathologically confirmed endometriosis may have no pain whatsoever [132–134]. Therefore, closer physiological insights into the complex pain mechanisms associated with endometriosis are warranted in order to improvise a newer and improved mechanism-based evaluation [118,119,135,136]. By developing a tangible model incorporating the understanding of central and peripheral sensitization with that of underlying inflammatory processes in a unified scoring scale of pain threshold, we may be in a better position to select a treatment paradigm targeted to specific mechanisms and leave aside presently prevalent non-specific approach to treat endometriosis-associated pain, which may produce harmful side effects and have high long-term failure rates [119,135,137].

5.2. Endometriosis-Associated Infertility

Advanced endometriosis may lead to major pelvic adhesions blocking the release of oocytes and distorted pelvic anatomy that results in altered tubo-ovarian relationship and movement of gametes (oocytes and sperms), resulting in low rate of fertilization [138–140]. However, anomalous physiological signal emanating from biochemical and molecular imbalances in endometriosis is also a well acknowledged underlying cause of infertility seen in 50% of endometriosis patients with normal ovulation and normo-spermic partners [141]. Systematic review of clinical evidence reveals that stage III/IV endometriosis is associated with poor embryo implantation rates and pregnancy rates in women undergoing IVF treatment [142]. In Table 1, we have identified major factors that may be causally related to the incidence of primary infertility in endometriosis.

Table 1. Major pathophysiological factors causing primary infertility in endometriosis.

Factor	Reference [Reference No.]
• Disturbed folliculogenesis	Nakahara et al., 1998 [143]
• Luteinized unruptured follicle	Kaya and Oral, 1999 [144]
• Oocyte quality	Sanchez et al., 2016 [145]
• Adhesions	De Venecia, Ascher, 2015 [140]
• Dysfunctional uterotubal motility	Kissler et al., 2005 [138]
• Detrimental effects on spermatozoa	Reeve et al., 2005 [139]
• Peritoneal inflammation	Malvezzi et al., 2019 [85]; Anupa et al. 2020 [86]
• Progesterone resistance plus estrogen dominance	Sengupta et al., 2017 [5]; Anupa et al., 2019 [146]; Bulun, 2019 [147]
• Endometrial hostility	Sengupta and Ghosh, 2014 [148]; Lessey and Kim, 2017 [149]; Miravet-Valenciano et al., 2017 [150]; Lessey, Young, 2019 [151]
• Immune dysfunctions	Schatz et al., 2016 [152]; Jørgensen et al., 2017 [96]; Lin et al., 2018 [124]

Ovarian functions in endometriosis are greatly compromised with altered follicle morphology and functions in affected women [153,154]. Molecular data support the notion that the intra-follicular environment is affected with reduced steroidogenesis, reduced P450 aromatase expression, increased intracellular ROS generation and altered WNT signaling in the granulosa cells of women with endometriosis that may lead to poor retrieval of MII oocytes from the affected ovary with endometrioma compared to the contralateral healthy ovary [145,155,156]. Inflammatory changes that affect the peritoneal and the intra-tubal milieu are quite likely to adversely impact upon the process of oocyte fertilization and natural conception. The occurrence of fibrosis in ovarian endometrioma due to the inflammatory reaction caused by heme-induced oxidative stress and "burn-out" of early follicles by the local pelvic inflammatory environment have also been suggested as a potential causative factor leading to infertility [157,158].

Patients with endometriosis are often advised to undertake assisted reproductive technologies such as in-vitro fertilization (IVF) as one means of achieving conception [159]. Clinical pregnancy rates between endometriosis patients and controls were similar between stages I-II and controls, while it was markedly lower in stage III-IV endometriosis [156]. This supports the earlier observation of poor pregnancy rates in women with stages III/IV endometriosis following IVF/ICSI [160]. Freis et al. [161] have reported poorer embryo quality from patients with endometriosis in all stages (I-IV) of the disease, on the basis of embryo cleavage synchronicity in vitro. However, a subset of such failures in IVF clinics might have resulted from the lack of synchrony between blastocyst and endometrial developmental trajectories in diseased women [162].

A large body of evidence obtained from clinical and animal studies leads us to consider that an inflammatory condition can alter endometrial function during endometriosis, supporting an association between endometriosis and infertility [149]. An inflammatory niche that exists within the eutopic endometrium and in the peritoneal environment of women with diagnosed endometriosis (vide Figure 5) may adversely affect endometrial functioning towards supporting a viable pregnancy. Eutopic endometria of infertile women with endometriosis show unique genomic signature for inflammatory hyperactivity [163,164]. Specifically, pro-inflammatory cytokines, chemokines and receptors including CXCL1, CX3CL1, CXCL9, CXCL10, IL32, CXCR2, IL7R and adhesion molecules including ICAM3 and L-selectin are expressed at higher levels in the eutopic endometrium of infertile endometriosis patients as compared to fertile controls [163]. Eutopic endometrium collected from women in the "implantation window" of the secretory phase and diagnosed with primary infertility with stage IV ovarian endometriosis revealed a unique signature of upregulated CCL2, CCL3, CCL4, CCL5, CXCL10, FGF2, GCSF, IFNG, IL1, IL1RA, IL5, TNFA and VEGF and downregulated expression of IL18 compared with the control group [86]. Interestingly, IL18 may influence both Th1 and Th2 immune responses depending on overall cytokine milieu and thus can fine-tune the immune responses [165]. In the mid-luteal phase, stromal and endothelial cells of endometrium secrete IL15, Fn14, IL18 and TWEAK at specific levels that allow the recruitment and maturation of uNK cells for Th1-to-Th2 equilibrium which promotes immunotrophism and angiogenesis, while inhibiting inflammatory and cytotoxic pathways [166]. Continual exposure of eutopic endometrial cells to a pro-inflammatory niche such as it occurs in the peritoneal microenvironment in endometriosis suggestively influences DNA methyltransferase I (DNMT1), cell surface cytokine receptors, activation of several protein kinases (AKT, ERK1 and MAPK), and activation of NF- B, which collectively may invoke endometrial hostility to embryo implantation [167].

6. Physiological Basis of Management of Endometriosis-Associated Medical Problems

Endometriosis is a systemic disorder associated with heterostasis in neurological, metabolic and inflammatory processes with two major stress factors—pain and infertility. Though nearly 10–15% of the general female population suffer from endometriosis and 25–50% women suffer from infertility and more than 70% from chronic pelvic pain [33], this reproductive disorder remains a huge challenge to clinicians; the available pharmacological and surgical approaches that can provide relief to two-thirds of the women suffering from pelvic pain due to endometriosis, however, are associated with frequent recurrence [168–171]. Vercellini et al. [172] proposed the use of medical treatments such as oral contraceptives (OCs), which reduce the recurrence rate of post-operative endometrioma and are essential for long-term therapy that may limit further damage to future fertility with a reduction in the risk of endometriosis-associated ovarian cancer. In Table 2, we provide a list of the currently available treatment strategies mainly for the management of endometriosis-related pain and the handling of disease recurrence, which are based on proven clinical studies. Clearly, further molecular studies are required to understand the link between endometriosis and its role in the onset of ovarian carcinoma [11] and to establish the phylogenetic basis of endometriosis disease and its association with ovarian cancer [173].

Table 2. Medical strategies for the management of endometriosis-associated pain and infertility.

Therapy	Major Observations [Reference No.]
Danazol	Danazol is a weak androgen and anabolic steroid, a weak progestogen, a weak antigonadotropin, a weak steroidogenesis inhibitor and a functional antiestrogen [174]. A large number of patients do not report any significant relief of pain. Moreover, 1 out of 3 patients reported of recurrence of pain at the end of treatment [175–177]. According to some reports the treatment may reduce endometriosis related pain but has androgenic effects and causes cysts and infertility [178].
Gestrinone	Gestrinone is a mixed progestogen and antiprogestogen, a weak androgen and anabolic steroid, a weak antigonadotropin, a weak steroidogenesis inhibitor, and a functional antiestrogen [174]. 1 out of 4 patients did not report any significant relieve of pain. Also, 1 out of 4 patients reported of recurrence of pain at the end of treatment or pain remaining at the end of treatment [179,180]. The main side effects are similar but less intense than those caused by danazol [181].
GnRH agonist	14% of patients did not experience any change in pain, while 40% patients experienced non-pain status remaining at end of treatment and 34% experienced recurrence at the end of treatment [43]. GnRHa alone has adverse side effects of estrogen deficiency and reduction in bone mineral density and sexual functioning [182,183].
GnRH antagonist	Reported studies conducted in industry setup. With Elagolix, 19% of patients did not experience any change in pain [184,185]. Effective in improving dysmenorrhea and non-menstrual pelvic pain with significant lessening of fatigue, however, with associated hypoestrogenic adverse effects [186,187].
GnRH agonist (Leuprolide) + progestin (NETA)	61% pain reduction during treatment and 52% continued pain reduction after stopping treatment. 80% had at least one long term side effect more than 6 months after the completion of treatment [188].
Synthetic progestogen	With dienogest, pooled analyses from clinical studies showed its tolerability with good safety profile and progressive improvement in pain scores in Caucasian [189] and Chinese population [190]. Comparable results were reported with norethindrone acetate [191]. Reductions in serum high density lipoproteins with use of norethindrone acetate and minor loss of bone density with dienogest are issues of concern [191].
CHCs, COCs, POCs	CHCs and POCs are effective for the relief of endometriosis-related dysmenorrhoea, pelvic pain and dyspareunia and for improving the quality of life. A few COCs (ethinylestradiol/norethisterone acetate, ethinylestradiol/desogestrel and ethinylestradiol/gestodene) decreased risk of recurrence. Additional well-designed, blind, comparative trials required for effective management of endometriosis-related pain. For details, see Grandi et al. [192].
Letrozole	Letrozole is an orally active, nonsteroidal, selective aromatase inhibitor used in the treatment of hormonally responsive breast cancer after surgery [193]. It may be administered in combination with oral contraceptive pills, progestogens or GnRH analogues for treating endometriosis associated pain to the patients with pain from rectovaginal endometriosis, and also to the patients who are refractory to other medical or surgical treatments it can be considered prescribing aromatase inhibitors [194,195]. Major side effects are hot flushes, myalgia and arthralgia [196]. It is as yet not globally approved.
NSAIDs	NSAIDs are the most commonly used over the counter drugs for the management of endometriosis related pain and dysmenorrhea; the evidence to indicate whether NSAIDs such as naproxen sodium are indeed effective for the management of pain caused by endometriosis is as yet inconclusive. There are insufficient studies to prove either way, as well as to prove the efficacy and safety of NSAIDs in the management of pain in endometriosis [197].

CHC, combined hormonal contraceptive; COCs, combined oral contraceptive; GnRH, gonadotropin-releasing hormone; NETA, norethindrone acetate; NSAID, nonsteroidal anti-inflammatory drug; POC, progestin only contraceptive.

Endometriosis-associated infertility is attributed to several mechanisms as described above. There are no clear-cut directions available for management strategies to tackle endometriosis-related infertility as one of the major stress points to patients with ancillary social and inter-personal issues. The management of endometriosis-related infertility thus remains quite challenging and a highly debated issue [198]. A systematic review and meta-analysis to examine the pregnancy rates obtained from four types of treatment on infertile women diagnosed with ovarian endometriosis, viz., surgery + ART, surgery + spontaneous pregnancy, aspiration ± sclerotherapy + ART and ART alone, concluded that treatments should be administered on the basis of patient's clinical condition and must be individual-oriented with the purpose of relieving pain, improving fertility or both [199].

The classification of endometriosis as per the revised American Society for Reproductive Medicine (rASRM) guidelines [200] allows for the staging of endometriosis, while the ENZIAN classification system [201] supplements the rASRM classification especially for deep infiltrating endometriosis and its severity state. However, neither the rASRM nor the ENZIAN guidelines provide any direct prediction on the pregnancy rates.

As explained in Figure 7, the Endometriosis Fertility Index (EFI) proposed by Adamson and his group however provides a validated classification system that helps to predict the clinical outcome of pregnancy [202,203]. Two recent reports indeed supported the recommendation of the EFI scores demonstrating that it reflected a statistically significant positive correlation with pregnancy outcome; the higher the EFI score, the better was the reproductive outcome [204,205]. In fact, the EFI has been recommended as a valid clinical tool to predict the fertility outcome for women following surgical staging of endometriosis and may be used toward developing suitable treatment plans for infertile women with endometriosis [206]. A prospective inter-/intra-agreement study also suggests its use as an effective clinical tool for post-operative fertility counselling and its management [207]. Johnson et al. [206] while discussing the World Endometriosis Society consensus on the classification of endometriosis suggested of a toolbox approach that included the rASRM guidelines, the ENZIAN system and the EFI staging systems as appropriate.

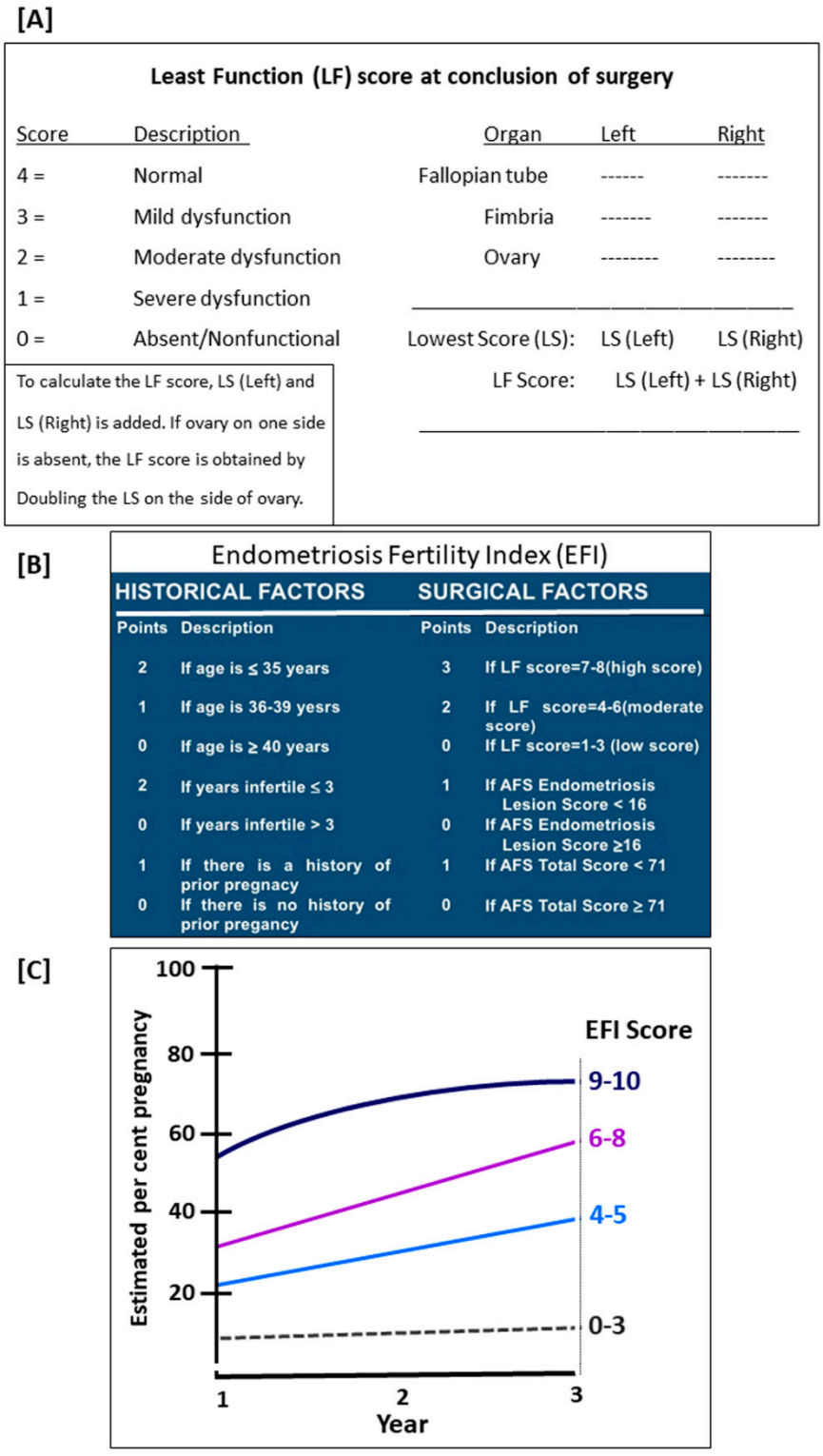

Figure 7. Endometriosis Fertility Index (EFI), which is calculated from Least Function (LF) scores from surgical conclusion (**A**) and then from total historical factors and surgical factors from LF score and AFS endometriosis score (**B**), appears useful in predicting pregnancy outcome (**C**) in endometriosis patients. Details have been given in the text. Adapted from Adamson [202], Cook and Adamson [203].

During early pregnancy the circulating progesterone is inversely correlated with the circulating glucocorticoids [208]. Moreover, exposure to stress during pregnancy is associated with lower circulating progesterone concentrations [209]. Stress-induced glucocorticoid secretion inhibits pituitary

hormone secretion, resulting in decreased ovarian progesterone synthesis [64,210]. While invasive studies related to stress are not permissible during the time of pregnancy establishment (i.e., first two to three weeks following ovulation when embryo implants and placentation is initiated) in women for ethical considerations, in a year-long prospective study, Nepomnaschy et al. [211] examined the urinary cortisol levels during the first three weeks of gestation—a critical early period of pregnancy establishment—and observed that pregnancies resulting in spontaneous abortion were characterized by increased maternal cortisol linking the higher levels of this stress hormone with a higher risk of early pregnancy loss in these women. In a longitudinal study of stress and women's reproduction in a Kaqchikel Mayan community living in rural Guatemala, these authors further observed that higher urinary cortisol levels were associated with significantly lower progestin levels during the follicular phase, and also during the time window between days 4 and 10 after ovulation [212]. Successful human pregnancies occur with implantation of the conceptus on days 8 to10 post-ovulation, the risk of early pregnancy loss being observed with late implantation [213]. In women, the mid-luteal phase known as the "window of implantation" may be identified by the levels of serum progesterone and estradiol-17β, both higher than that found in non-conception cycles [214–217]. A local ambience of adequate progesterone and its actions in the mid-luteal phase of a conception cycle is *sine qua non* for embryo development and differentiation, embryo implantation and successful pregnancy establishment [148,218–222]. An inverse association therefore emerges between cortisol and progesterone in the mid-luteal phase of women under stress that creates an endometrial milieu non-conducive for embryo implantation, and it adversely affects fecundity.

Alongside the possible interference from a compromised progesterone to cortisol ratio in the systemic level, local heterostasis in the progesterone receptor (PR) action in eutopic endometrium during endometriosis appears to be critical. It is well established that progesterone responsiveness in the endometrium is mediated by the coordinated actions of two isoforms—PRA and PRB—transcribed from two different promoters of the single PR gene with the absence of 164 amino acids at the amino terminus in PRA compared to PRB [223]. The human PRB functions as an activator of progesterone-responsive genes, while PRA is transcriptionally inactive and additionally functions as a strong transdominant repressor of PRB and ER transcriptional activity [223]. In normal endometrium, the PR isoforms are evenly distributed in the proliferative phase, while PRB is the predominant isoform in the secretory phase, and that leads to a higher PRB:PRA ratio in the secretory phase endometrium [224]. While investigating the functionality of the PR isoforms, Wetendorf et al. documented that infertility occurs in a mouse model that constitutively expresses PRA, and that down-regulation of PRA isoform during the window of receptivity was necessary for producing a receptive environment for the attaching embryo [225]. In patients with endometriosis, the environment of eutopic endometrium appears to undergo a loss of the normal luteal-phase dominance of progesterone resulting in progesterone resistance and estrogen dominance [149,167]; human endometrial fibroblasts display progesterone resistance in the endometrial niche in endometriosis [164]. Such dysregulated progesterone action may result in hyperplastic noise in the endometrium [86,226]. In patients with primary infertility and moderate to severe ovarian endometriosis, secretory phase endometrium generally exhibits higher intracrine estradiol-17β, dysregulated 17βHSD1 expression, higher PRA:PRB ratio and lower ERβ compared with infertile patients who are free of the disease [146]. Low ERβ levels were reported in cells of the eutopic endometrium from patients with endometriosis and were found to be positively correlated with increased telomerase expression to indicate a persistently greater proliferative phenotype [227,228]. Such cellular phenotype due to hyper-estrogenism and progesterone resistance during the secretory phase of the menstrual cycle appear as hallmarks of secretory phase eutopic endometrium of infertile patients with ovarian endometriosis [146]. It is generally known that endometrial competence for promoting normal development and differentiation of preimplantation stage embryo and its implantation are dependent on progesterone actions [148,149]. As modelled in Figure 8, progesterone resistance results in abrogation of a normal secretory-phase differentiation phenotype, and an associated hyper-estrogenism induces proliferative phenotype in the secretory

phase eutopic endometrium. These factors indeed appear to be two predictable movers causal to infertility in patients diagnosed with endometriosis [146,167]. These findings are now well supported by clinical evidence based on a systematic review that stage III/IV endometriosis is associated with poor implantation rates and poor clinical pregnancy rates in women undergoing IVF treatment [142]. In a recent study, Flores et al. [229] reported that progesterone receptor status of eutopic endometrium and ectopic lesions may be considered as one option to individualize a progestin-based therapy for a novel, targeted, precision-based approach to treating endometriosis-related infertility due to an insufficiency in endometrial receptivity. However, we consider that in this direction due caution is necessary to avoid a selection bias with likely confounding results if sampling is not done properly in accordance of the EPHect guidelines [230] as revealed in a recent study [146]. Prospective studies are necessary to determine the degree of response to progestin therapy only if the local mechanism prevails over the systemic mechanism.

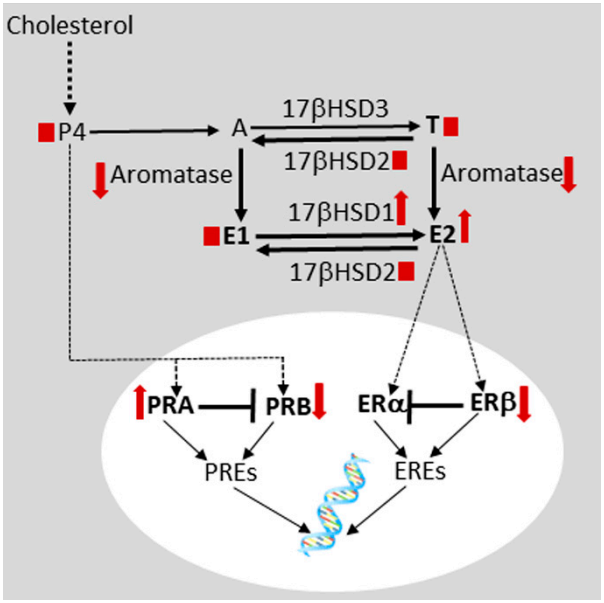

Figure 8. A working model of steroid metabolism and actions in eutopic endometrium during moderate (stage III) to severe (stage IV) ovarian endometriosis that draws upon three major factors: (i) intracrine levels of progesterone (P4) and estradiol-17β (E2), (ii) nuclear receptors for P4 (PRA, PRB) and E2 (ERα, ERβ) and their respective ratios and (iii) the steroidogenic pathways in endometrium. Combinatorial effects of increased tissue E2 from aromatase-independent pathway of elevated 17βHSD1, increased PRA:PRB, decreased ERβ induces a strong bias towards estrogenic dominance and progesterone resistance in the secretory phase endometrium of the patients with stage III–IV ovarian endometriosis. These changes in the eutopic endometrium disrupt its secretory phase maturation with increased cell proliferation, cell migration, loss of decidual cell competence and adventitious inflammatory responses resulting in its incompetence to embryo implantation. ⬆, increased; ⬇, decreased; ■, no change. E1, estrone; E2, estradiol-17β, ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; 17βHSD, 17beta hydroxysteroid dehydrogenase subtype; P4, progesterone; PRA, progesterone receptor isoform A; PRB, progesterone receptor isoform B; PREs, progesterone response elements. For details, see Anupa et al. [146].

7. Potential Impact of Patient Centric Multidisciplinary Healthcare in Endometriosis

Patient-centered care now appears to be imperative to promote the health-related quality of life of women with endometriosis and associated pain and infertility [231,232]. Patients experiencing endometriosis value 'patient-centric care' notably in two important realms: "timely diagnosis" and "being believed and respected by staff" [233]. It has been reported that such approach when carefully followed assure several important aspects of disease management [234]. It provides continuity as a foundation for a biopsychosocial approach whereby the medical focus shifts from treating the patient's

body as a clinical object to the human being. Also, careful and transparent conversation between the patient and healthcare provider with sensitivity allows during their encounter for thoughtfulness, reflection and responsiveness in both sides [234]. These attributes allow for building up a productive interaction channel between "informed, active patient" and "prepared, proactive practice team" which along with mutual transparency allows for building mutual respect, relevance and coherence at the subjective level and the higher chance of early diagnosis and treatment success at the objective level [234–236]. Thus, the emerging notion that women in endometriosis with associated stress are in need of long-term care and support for improving their quality of life, as well as, for their physiological, psychological and social wellbeing through patient-centric approach delivered by multidisciplinary healthcare team of experts that would include general physicians, specialists, psychologists, specialist nurses, sexologists and social workers appears sound and tenable, and in fact due to be practiced without any further delay [33,233,235,237–240].

8. Conclusions

Despite limitations typically noted in a narrative review, a few of the important conceptual issues regarding endometriosis-linked stress identified in the presents review appear to be meaningful to the stake holders. It is evident that endometriosis is a complex chronic inflammatory disease of unclear etiology with very little curative treatment available. A large number of reproductive-aged women suffer from the disease and its associated pain, infertility and a range of symptoms, which can be confusing both for the patient and the care provider, often leading to an unfortunate delay in diagnosis and initiation of treatment. Available medical strategies for the management of endometriosis are limited in providing long-term relief, while endometriosis-related array of symptoms affects the productivity of the women with the disease leading to social withdrawal, psychological negativity and broader reductions in the quality of life. It is now evident that the multi-dimensional aspect of endometriosis-associated stress deserves serious and multi-faceted attention in reproductive medicine. On the one hand, we need to provide improved medical and surgical management for organically treating hyper-inflammatory state and associated pain and infertility during endometriosis; there is also an emergent need to address the negative impact of endometriosis on the woman's quality of life through patient-centric chronic care and management system. Finally, in Figure 9 we forward a comprehensive diagram to provide critically important pointers toward future research studies necessary to address various translational aspects of stress physiology of endometriosis.

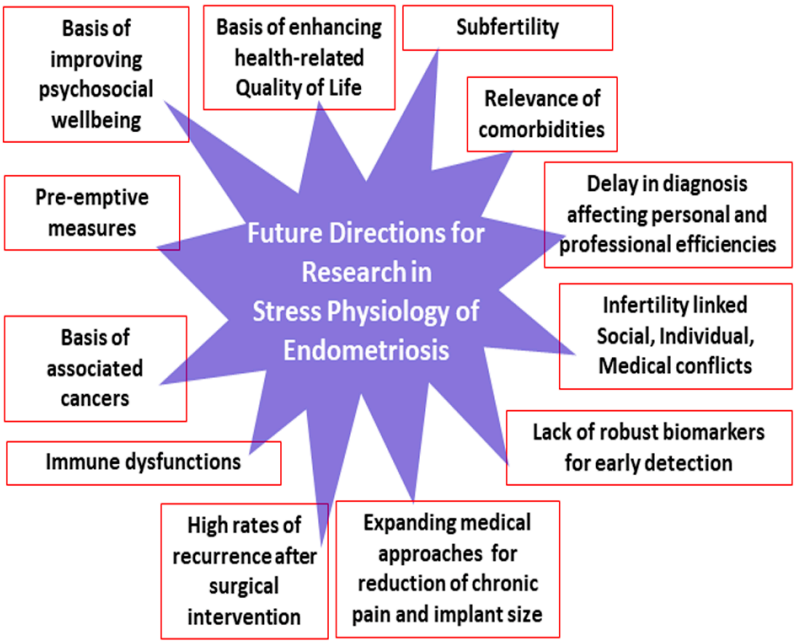

Figure 9. A comprehensive scheme of critically important paradigmatic pointers towards future research studies necessary to address integrative and translational aspects of pathophysiological basis of endometriosis-linked stress and associated pain, infertility and comorbidities.

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