REVIEW PAPER

From Hormonal Dysregulation to Ovarian Carcinoma: Pathophysiology of Cramps and Fibroids with Insights from AI/Machine Learning and Phytonanotherapeutics

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Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

ABSTRACT
Menstrual cramps, uterine fibroids, and ovarian carcinoma are not seen as independent gynaecologic disorders but as stages of a biologically related series which occurs due to chronic destabilization of the estrogen-progesterone homeostasis. Chronic steroid-signaling disequilibrium results in the activation of NF-κB, COX-2, pro-inflammatory cytokines, prostaglandin F2 leading to uterine hypercontractility, angiogenesis, and cellular proliferation. These changes are manifested as dysmenorrhea and bleeding and promote the growth and development of fibroid. With time, this environment establishes a tumor-promoting pelvic field in genetically or epigenetically predisposed women MELD12/HMGA2 changes, BRCA-related DNA-repair errors, estrogen metabolism or stable DNA-methylation/histone marks that promote the development and progression of epithelial ovarian carcinoma. Molecular, systems-biology, epidemiologic, and clinical data combined demonstrate that cramps-fibroid-cancer continuum pathways are the estrogen-progestogen-oxidative-stress network, NF-κB/COX-2/prostaglandin-mediated inflammation, TGF-β-dependent fibrosis and mechanotransduction, and est The models of genomic, transcriptomic, epigenomic, and proteomic data stratify patients into high and low risk groups, based on fibroid growth propensity, level of dysmenorrhea, and prognosis. Nanotechnology Therapeutics: The nanotechnology-based therapeutics, phytonanotherapeutics, e.g. curcumin, resveratrol, quercetin, and green-tea catechins to target TGF-β/SMAD, IGF, VEGF. Together with multi-omic cohorts, wearable real-time feedback, and smart menstrual diagnostics, AI-enhanced decision support, and nano- and phytonanotherapeutic trials carried out with high ethical and equity standards, this paradigm shifts the disjointed, symptom-based care to comprehensive, preventive gynaecologic health, in which cramps are early warning signals, fibroids are reversible.

Keywords: *Hormonal dysregulation, Chronic inflammation, Uterine fibroids, Ovarian carcinoma, Artificial intelligence, Phyto-nanotherapeutics.*
How to cite this article: Dixit V, Gupta K, Singh T, Bagh A, Sharma NR, Verma AK. From Hormonal Dysregulation to Ovarian Carcinoma: Pathophysiology of Cramps and Fibroids with Insights from AI/Machine Learning and Phytonanotherapeutics. Int J Drug Deliv Technol. 2026;16(41s): 1123-1157. DOI: 10.25258/ijddt.16.41s.118
Source of support: Nil.
Conflict of interest: None

GRAPHICAL ABSTRACT

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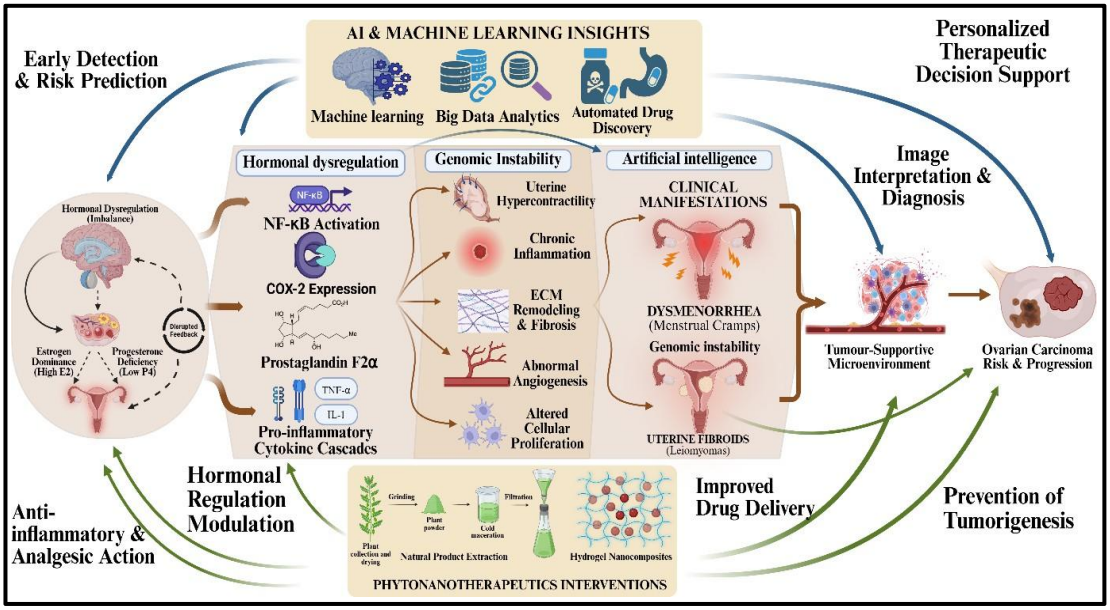

1. INTRODUCTION

1.1 World morbidity of menstrual cramps fibroids and ovarian cancer

Uterine fibroids, also known as leiomyomas, are benign neoplasm of the female reproductive tract originates from smooth-muscle of the myometrium, and one of the most common causes of gynaecologic morbidity in the reproductive and perimenopausal age groups[1]. Imaging and histopathologic criteria utilized in epidemiologic studies show that 70-80 percent of women develop fibroids at age 50, but elevated percentages of fibroids goes unnoticed, thus leading to underestimation in routine hospital-collected statistics of the true population toll[2]. The currently well-defined risk factors include: early menarche, nulliparity, obesity, African ancestry, family history and chronic hormonal imbalances between estrogen and progesterone, along with an increasing appreciation of environmental causative factors such as endocrine-disrupting chemicals and long-standing psychosocial stress[3]. All these converge to signaling pathways which amplify myometrial growth, deposition of extracellular-matrices as well as angiogenesis[4]. Having excessive or prolonged bleeding during menstruation, dysmenorrhea, pelvic pressure, dyspareunia, infertility issues , and poor outcomes of pregnancy, including miscarriage, malpresentation, and preterm birth, symptomatic fibroids are one of the most frequent reasons of hysterectomy in the world, making them a significant source of gynaecologic surgical volume, blood transfusion, and anemia-related disability, especially in low-resource countries where access to minimally invasive treatments is poor[5]. Dysmenorrhea as a painful menstrual cramp is one of the most common gynaecologic disorders in the world with an estimated 50-90 in comparison to age, diagnosis criterion, and location[6]. Primary dysmenorrhea occurs in the absence of structural or inflammatory pathology, and is mediated by an excess of prostaglandin F2-α and E2 production leading to severe uterine hypercontractility, transient ischemia and pain; secondary dysmenorrhea represents underlying structural or inflammatory pathology, most commonly endometriosis, adenomyosis and fibroids[7]. Surveys on bulky populations of adolescents and young adults are conducted regularly in Asian, African, European, and American schools and universities, all finding dysmenorrhea to be causing short-term school and work absenteeism, lowered concentration, decreased physical activity, and lowered quality of life, accompanied by increased anxiety, depressive symptoms, and sleeplessness[8]. These results demonstrate that not only is menstrual pain a minor inconvenience, it is impactful, often underappreciated factor that will lower productivity and promote psychosocial stress[9]. Although ovarian cancer is much rarer than fibroids or dysmenorrhea, the likelihood that it fails to exhibit symptoms early, has a deep location in the pelvis, and no definite screening testing makes it the most lethal gynaecologic malignancy; more than two-thirds of patients, therefore, present with metastatic disease[10]. Recent burden-of-diseases analyses estimate about 300,000 new cases of ovarian cancer-related cases and exceeding 200,000 deaths every year across the world with age-standardized incidence being highest in high-income nations but with poorer results of late-presentation, minimal access to subspecialty surgery, and limited availability of platinum agents, PARP that inhibits, and biologics[11]. The most common histologic subtype is high-grade serous carcinoma which is highly linked to malfunctioning of homologous recombination mainly by means of germline or somatic mutations of BRCA1 and BRCA2 and other DNA-repair genes but lifestyle issues, reproductive history, and a potential previous hysterectomy or fibroid diagnosis can also influence vulnerability[12]. Under all these circumstances, gynaecologic health has sweeping racial, ethnic, and socioeconomic patterns: women of African origin get diagnosed earlier, have larger and more numerous fibroids, have a higher probability of undergoing hysterectomy at younger ages, and incur higher stage distributions, fewer treatment access and survival of fibroids than women of other descent, and the marginalized population face shorter finer adjustments to stage access, treatment availability

and survival of ovarian cancer, under all of which there is a considerable disparity across regions and social environments. Combined with these trends, the cramps that women have during their menstrual period, fibroids and ovarian cancer represent a huge burden in the world that is disproportionately prevalent and poorly managed by the current existing care systems[13].

1.2 The Hormone-Cancer continuum: Justification to study as one

Hormonal control offers a mechanistic axis of harmony between benign conditions of the gynaecologic system, including dysmenorrhea and fibroids, and cancerous ones, including high-grade serous ovarian carcinoma, and the continuum offers a format in which these distinct diseases can be studied within the same pathophysiologic context, rather than isolated studies[14]. It is in these pathways that high levels of oestrogen and progesterone receptors or a disruption in the oestrogen and progesterone receptor signalling regulate endometrial proliferation, differentiation and shedding, and myometrial contractility and extracellular-matrix remodelling; and, when circulating in excess, high concentrations of these receptors, together with the abnormal co-regulation of other pathways, mediate proliferation and fibrogenesis in the endometrium, and deposition of collagen-rich matrix micromole[15]. More recent systems-biology investigations outline a system of oestrogen-progestogen-oxidative-stress (E PO S) in fibroids where sex steroids and reactive oxygen species mutually feed-back onto each other: the oxidative stress induced by sex steroids and progesterone by modulating mitochondrial activity and antioxidant capability is amplified by oxidative damage that repair and enhances sex-steroids-receptor signalling to form a self-amplifying loop that lets fibroid growth withstand additional genomic and epigean[16]. Similar themes are found in ovarian carcinogenesis, in which chronic ovulation, continuous repair of the ovarian surface and fimbrial epithelium and recurrent exposure to inflammatory mediators, iron, and reactive oxygen species in the follicular liquid results in a microenvironment favouring DNA double-stranded breaks, chromosomal aberrations and malignant transformation, especially in the face of inherited or acquired mutations in BRCA-mediated repair of DNA damage[17]. A second intersecting axis between cramps, fibroids, and cancer is therefore inflammatory signalling: in primary dysmenorrhea overproduction of prostaglandin and cytokines during menstruation would produce acute pain and local ischemia; in fibroids and endometriosis macrophage-rich cytokine-rich local environments would stimulate angiogenesis, nociceptor sensitization and remodelling; in ovarian cancer, chronic IL-6, TNF-α and chemokine induced angiogenesis, immune[18]. Epidemiologic studies, including large cohort and case control investigations, already show that women who have had fibroids or a hysterectomy have altered risks of developing ovarian and endometrial cancer , even when controlling for the effects of age and the reproductive variables listed, relatively recent reviews suggest that shared hormonal, metabolic, and inflammatory pathways instead of a direct malignant progression of fibroids is likely to be the reason for the associations[19]. All of this seems to be served by endocrine-disrupting chemicals, hyperestrogenism due to obesity, and long-lasting low-grade inflammation that leads to the heightening of risks with both benign proliferative and hormone-sensitive tumors[20]. Although the causal mechanisms and timing have not been clearly defined yet, the available mechanistic and epidemiologic data give solid support to the hypothesis of an integrated hormone cancer continuum wherein menstrual pain, fibroids and ovarian carcinoma are considered to be the various manifestations of steroid-hormone overregulation and inflammatory stress mechanisms in the same axis of reproductive organs, and with striking consequences on prevention, surveillance, and treatment[16].

1.3 Gynaecologic oncology technological revolution

It is and will continue to be against this backdrop of massive disease burden and pathophysiology commonality that a technological revolution is occurring in gynaecologic oncology, with the far corner being artificial intelligence, machine learning, multi-omeics, and advanced nanomedicine, and that it is starting to fill long-standing gaps of early diagnosis and targeted therapy that has limited progress in both benign and malignant conditions[21]. Deep learning imaging systems, e.g., convolutional neural networks, attention-based models are trained onto large data sets of transvaginal ultrasound, CT, and MRI[22]. These systems automatically identify structures of the uterus and adnexa[23]. They are able to distinguish between benign and malignant ovarian masses[24]. In addition, they can forecast histological subtype and homologous recombination deficiency and transform routine scans into detailed quantitative radiomics signatures that provide information on subtle textural and vascular differences that are not visible to the naked human eye[25]. Radio genomics builds on this by combining radiomic with genomic and transcriptomic results to infer tumour biology as non-invasive with an inference of BRCA/HRD predictive capability, molecular subtype, and likely platinum or PARP responsivity using baseline radio genomics thereby providing a pathway to pre-emptive risk stratification, more rational choice of therapy without repeat tissue biopsies[26]. Parallel AI assistance in liquid-biopsy systems uses machine-learning classifiers on circulating tumour DNA, methylation patterns, exosomes, and fragmentome data in blood or in the ascetic biopsy to detect ovarian cancer at lower tumour fractions, follow clonal evolution, and indicate new resistance in near real-time; and related results are also being applied to detect inflammatory and hormonal signatures of severe dysmenorrhea and endometriosis, fibroids, explaining why blood-based systems have been proposed to detect and monitor benign progression of Outside diagnostics, predictive modelling with supervised and survival-analysis algorithms can combine clinical, hormonal, imaging, and genomic data to create specific risk scores in individual to either intervene surgically, increase systemic therapy, or sequencer novel agents[27]. Plant-derived nanomedicine-or phytonanotherapeutics-provides a supplemental approach that is especially

favourable towards both hormonally mediated and inflammatory gynaecologic diseases: loading pleiotropic phytochemicals including curcumin, quercetin, resveratrol, berberine, and *Nigella*-derived quinones into liposomes, polymeric nanoparticles, or gold and silver nanocarriers produced greenly may enormously enhance their solubility, pharmacokinetics, and tumour[28]. Ovarian cancer and fibroid model preclinical studies have demonstrated that these nano formulations have the ability to slow tumour growth, sensitize cells to both platinum and taxanes, inhibit inflammatory and angiogenic signaling, and spare normal tissues, suggesting that these nano formulations could be used as biological adjuncts or alternatives to traditional cytotoxics[29]. Most importantly, using AI-enabled natural product discovery systems and network pharmacology platforms, the systematic mining of large phytochemical libraries is now possible to locate combinations that target not only one node within the hormone-inflammation-oncogenesis network, but also combinations that can design nanocarriers with controlled size, surface charge, and ligand decoration for targeting the uterus or ovarian cancers[30]. In this future, AI/ML analytics and phytonanotherapeutics will be developed in combination as a toolkit to discover, classify and treat cramps, fibroids and other conditions - albeit with less toxicity than current one-size-fits-all approaches[31].

2. MENSTRUAL BIOLOGY DYSREGULATION IN HORMONES

Chronic disturbances to the hypothalamic-pituitary ovary (HPO) axis coordinating folliculogenesis, ovulation, endometrial cycling and menstruation cause hormonal disequilibrium in menstrual biology, which exaggerates inflammatory processes, alters uterine contractility and results in the replacement of reversible follicular cyclic plasticity by chronic pain and structural disease[32]. In physiological state, cyclic release of FSH and LH under the influence of pulsatile GnRH by hypothalamus stimulates follicular growth and mid cycle LH burst that results in ovulation; the dominant follicle secreted rising estradiol of the follicular phase, leading to endometrial proliferation, angiogenesis, and progesterone receptor up regulation and mid menstrual luteal progesterone causes steady and differentiating endometrial effects, a decrease in the excitability of the uterus, and when concentrations of progesterone decline at the late luteal phase, endometrial cells stimulate the NF-κB and COX-2 that result in surged prostaglandin F2 and PGE2 production, leukocyte recruitment (especially neutrophils and macrophages), matrix metalloproteinase activation, and controlled vasoconstriction and ischemia that cause menstrual shedding; in experimental mouse models of menstrual like, pharmacologic inhibition of either the NF-κB or COX-2 dampens bleeding and Case-control and menstrual fluid testing in primary dysmenorrhea reveals that in spite of no pelvic pathology evidence, hormonal signals result in a hyper-reactive response of COX-2/prostaglandin that can be effectively suppressed with NSAIDs by decreasing the magnitude and frequency of uterine contractions as well as raising the level of PGF2 and PGE2 on a baseline level. With cycles anovulatory or reduced length of luteal phases (as with cycle maturation in adolescence, perimenopause, obesity, PCOS, or chronic stress) there is a distortion in the timing and magnitude of estradiol and progesterone changes, with NF-κB, COX-2, prostaglandins, and cytokine activation unrestricted by a short and rapid perimenstrual period and continuing at low levels throughout the cycle[33]. This chronic, low-grade endocrine-immune activation over the years leads to extracellular matrix deposition, micro fibrosis, aberrant angiogenesis, and overall tissue stiffness in the myometrium and endometrium, which are subsequently observed data show to be associated with the increased prevalence of fibroids, abnormal enormity in actin myometrium and endometrium, and which in turn are found to feed it back and aggravate dysmenorrhea, abnormal uterine bleeding, and infertility. At the ovarian level, long-term low grade inflammation and hormonal dysregulation, well exemplified in PCOS and endometriosis are linked to follicular fluid IL-6, TNF-α, and reactive oxygen species (ROS), impaired steroidogenesis, disturbed follicle selection, and low oocyte quality, and longitudinal studies indicate that the inflammatory -hormonal microenvironment may collaborate with DNA repair errors to augment lifetime risk of epithelial ovarian carcinoma, thus entrenching cramps, fibroids, and ovarian malignancy in a shared HPO axis-response spectrum[34].

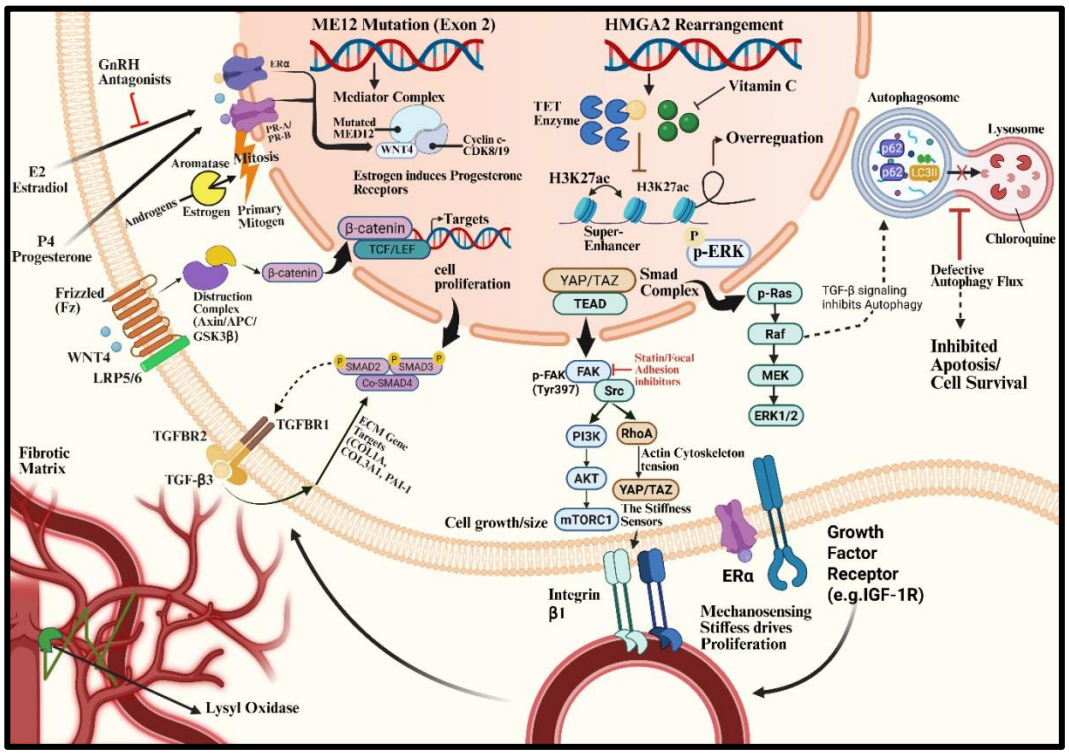

Figure 1: The dysregulation of the HPO axis hormonally and genetically by the menstrual cycle, fibroid growth, and ovarian cancer.

2.1. Effects of estrogen/progesterone imbalance in uterine physiology

The estrogen-progesterone imbalance lies at the heart of the spectrum of uterine physiology as estradiol and progesterone work together to control proliferation, differentiation, vascular remodelling and immune tone in the uterus, and even slight alterations in their ratio, timings or local metabolism can balance towards hyperplasia, fibrosis and pain[35]. Rather, Estradiol and its primary receptor-ERα (ESR1) stimulates endometrial and myometrial growth by promoting cyclins, growth factors and proto-oncogenes like (c-MYC) and enhances angiogenesis by up regulating VEGF, and activates progesterone receptors (PRA/PRB) to make tissues more receptive to luteal signalling and augments local aromatase activity raising intratissue estrogen levels higher than systemic levels[36]. Progesterone via its nuclear receptors normally opposes these actions suppressing further proliferation, stimulating stromal decidualization, stabilizing spiral arteries, and having anti-inflammatory effects which dampen NF-κB activation and down regulates COX 2 and IL-6 and other cytokines production outside the perimenstrual period[37]; progesterone also regulates myometrial excitability by down regulating the expression of ion channels and receptors and thus preventing excessive contractility during basal conditions[38]. The balance is however disrupted in most disorders of the uterus: obesity, exogenous estrogen exposure, anovulation and local aromatase overexpression augment estradiol exposure, whereas the differentiating and anti-inflammatory activities of progesterone are blunted by functional progesterone resistance, which is characterized by a reduction in PR expression, change in PR isoform ratios or post receptor signalling defects, and thus the uterus is persistently stimulated to proliferate and remodel, and is not able to have sufficient periods of In fibroids[39], on the other hand, estrogen and progesterone receptors are overexpressed, however, the overall outcome is proliferative and fibrogenic in that estrogen increases the expression of PR and local estradiol production and progesterone increases the proliferation of the smooth muscle cells and the production of ECM in the leiomyma-environment[40], a paradox such that has prompted a resetting of these hormonal interventions as protective to the disease promoting notwithstanding the presence of excess receptors and modified co regulator expression[41]. Ectopic lesions found in endometriosis have elevated local estrogen production, increased ER2, and strong progesterone resistance, such that estrogen enhances survival, invasion as well as inflammation and progesterone is unable to induce suitable decidualization or inhibit inflammatory gene expression, adding to lesion persistence and severe dysmenorrhea. In clinical practice, menstrual pain and bleeding are prevented by maintaining a more favourable estrogen/progesterone ratio as achieved by combined hormonal contraceptives, progestin only regimens, GnRH analogues, and selective progesterone receptor modulators and their efficacy supports the assumption that the estrogen/progesterone imbalance is not a peripheral event but a causative factor of uterine malfunction and physiologic prone to fibroid[42].

2.2 Molecular switches: NF-κB, COX-2 and prostaglandins and cytokine cascades

The central transducers orchestrating hormonal inputs to tissue level responses in the uterus and ovary are molecular switches centred on NF-κB, COX-2 and

prostaglandin, coupled with interconnected cascades of cytokines and their chronic dysregulation is the cause of menstruation based on hormones switching to cramps, fibroid development, and inflammatory based oncogenic risk[43]. Progesterone withdrawal in the endometrium causes rapid initiation of the canonical NF-κB pathway (p65/p50), resulting in nuclear translocation and promoter binding of PTGS2 (COX-2) and several pro inflammatory mediators; a seminal mouse menstrual like model revealed that NF-κB blockade suppresses COX-2 expression, prostaglandin production, leukocyte inflammation, and tissue breakdown extent, creating NF-κB as an upstream menstrual inflammation regulator[44]. Increased COX-2 induces a steep increase in both PGF2 alpha and PGE2 that agents through their G protein-coupled receptors in the myometrial cells to stimulate intracellular calcium, contractility, and vasoconstriction, and in women with primary dysmenorrhea, menstrual fluid analysis shows markedly higher levels of PGF2 alpha and PGE2 than in asymptomatic controls, and these rises are positively correlated with pain scores and uterine hyperactivity on imaging[45]. In addition to prostaglandins, NF-κB activation activates a wider cytokine cascade, including IL 1 and 2, TNF 4, CCL2, CCL5 the neutrophils and macrophages that migrate to the endometrium and myometrium, augment local inflammation, angiogenesis, and the expression of matrix metalloproteinases that are involved in tissue breakdown and remodelling; NF-κB activation in endometriosis and adenomyosis becomes chronic not cyclical and maintain the survival of ectopic There is more crosstalk between NF-κB signalling and estrogen signalling to complicate this: estrogen can increase NF-κB dependent transcription in some cell types, and NF-κB can in turn increase ER activity and co regulator recruitment, i.e. hormonal dysregulation and inflammatory stimulation feed off each other in endometrial cells and in myometrial cells[46]. Corresponding pathways play a role in the ovary, with follicular fluid and ovarian tissue in disorders like PCOS and endometriosis exhibiting increased TNF-α, IL-6, and reactive oxygen species, which through NF-κB-mediated and other DNA repair defect-dependent mechanisms disturb granulosa cell activity, weaken oocyte quality, and promote stromal fibrosis and aberrant angiogenesis; cumulative effects of which over time may cooperate with BRCA related or other DNA repair defects to create an environment favour[47].Therefore, NF-κB, COX-2, prostaglandins, and cytokines constitute a general mechanistic junction point where hormonal signaling is translated into acute menstrual shedding, and which when overactivated consistently over time under estrogen progesterone imbalance settings causes a continuum of dysmenorrhea to fibroids and may even put people at risk of long term reproductive and cancerous risk[48].

2.3 Effect on the myometrial, endometrial and ovarian tissue homeostasis

The interactive effects of hormonal dysregulations together with the inflammatory and prostaglandin mediators of hormonal dysregulations on myometrium, endometrium and ovarian tissue homeostasis are progressive and multi layered, changing normal self-renewable and cyclic tissues to chronic pain, fibrosis and neoplastic changeability adductive sites[49]. Estradiol and progesterone relate the expression of calcium channels, oxytocin and progesterone receptors, connexin-43-receptor-based gap junctions and cytoskeletal structures in the myometrium leading to more tuned uterine contractility and coordination in implantations; sustained prostaglandin overload and exposure to cytokines in dysmenorrhea and endometriosis favor this system to hypercontractile, high-basal-tone and episodic ischemia-reperfusion injury that Chronic estrogen dominance or progesterone resistance in the endometrium interferes with the normal proliferation secretory change and strictly regulated menstruation with the end result of partial shedding, frail or hyperplastic mucosa, aberrant spiral artery remodeling and incomplete repair; all of which make these areas more susceptible to implantation and form endometriotic lesions[50]. Subsequently, the sustained process of NF 5B activation and exposure to cytokines also reconfigures the endometrial immune environment to suppress NK cell cytotoxicity, polarize macrophages to M2 like and pro repair sub phenotypes, and facilitate the expansion of regulatory T cells, contributing to the loss of immune control of aberrant cells in the endometrium or tubo-ovarian epithelium[51]. In the ovary, low grade chronic inflammation and hormonal imbalance transforms the microenvironment in stromal and follicular cells: augmentation of IL-6, TNF-α and reactive oxygen species in the follicular fluid modify granulosa and theca cell membrane activity, alter the steroidogenesis, encourage stromal fibrosis and abnormal angiogenesis, and disrupt follicle selection and ovulation which has been observed in PCOS, ovaries with endometriosis, and aging ovaries[52]. Such microenvironmental changes, when combined with inherited or acquired defects in homologous recombination or other DNA repair pathways, may contribute to the accumulation of mutations and epigenetic alterations of the fimbrial and ovarian surface epithelium, over time, to develop high grade serous ovarian carcinoma, now believed to develop in the fallopian tube in most cases; hormonal deregulation and resultant inflammatory and mechanical consequences of the uterus and ovary is thus a coherent mechanistic continuum[53]. Figure 1 describes all the mechanisms discussed in above sections 2.1,2.2 and 2.3.

3. MENSTRUAL CRAMPS (DYSMENORRHEA) AND PATHWAYS OF PAIN

3.1 PFG-2-α overproduction causes hypercontractility of the uterus and ischemic pain

The pathogenic biochemical of the classical paradigm of classical hypercontractility of the uterus-ischemia of primary dysmenorrhea is an overproduction of PGF2a, where a physiological mechanism of menstruation is forced to pathologic levels[54]. Lysosomal and cytosolic phospholipase A2 is activated in endometrial stromal and epithelial cells in response to sharp falls in progesterone levels during the late luteal phase, releasing arachidonic acid (AA) in amounts greatly increased in dysmenorrheic women as compared to asymptomatic controls, and then

redirected into cyclooxygenase pathways, with COX-1 sustaining low amounts of prostanoid and COX-2 becoming highly induced during the time around menstruation, as a result of combined actions of COX-2 oxidizes AA into the unsteady intermediate, PGH2, which gets rapidly converted by tissue specific synthases into prostanoids, most notably PGF2 alpha and PGE2, that amass in menstrual fluid and perivascular spaces, and histologic and molecular evidence both support the high sensitivity of dysmenorrhea to COX-2 inhibiting NSAIDs. PGF2alpha stimulates mainly FP (PTGFR) receptors on myometrial and uterine vascular smooth muscle leading to Gq-PLC- β signalling, inositol trisphosphate (IP3)-mediated Ca^{2+} release through intracellular stores and strong and even tetanic myometrial contractions capable of generating intrauterine pressures up to 150-200 mmHg, much higher than during painless cycles, and inducing vasoconstriction of uterine arteries and arterioles[6]. These large amplitude, high frequency contractions squeeze the intra-myometrial vessels and dramatically decrease uterine blood flow to cause ischemia and hypoxia of the uterine wall; followed by transient reperfusion with partial relaxation, creating an ischemia-reperfusion cycle that triggers anaerobic glycolysis (lactate buildup) and acidosis and production of reactive oxygen species, which in turn further sensitize the nociceptive afferents[55]. Synthesis of PGE2, which is produced simultaneously with that of the PGH2, is mediated by EP receptors, especially EP3, in the uterus and those of the pelvic sensory pathways to modulate contractility, but, most importantly, to lower the activation threshold of peripheral nociceptors and dorsal horn neurons, which enables the occurrence of contractions that would otherwise be perceived as pressure to be frankly painful[56]. The Menstrual effluent literature demonstrates consistently elevated concentrations of PGF2 and PGE2 and a higher PGF2α:PGE2 ratio in women with primary dysmenorrhea and pain scores are positively correlated with a ratio with the ultrasonography based measures of uterine hypertonicity and contraction frequency, therefore, giving support to a dose response correlation between prostaglandin overload, uterine hypercontractility and the degree of ischemic pain[57]. Combining mechanical distortion of forceful contractions, ischemia induced acidosis, and high local concentrations of PGF2α and PGE2 at the uterine afferent, combination of all such changes is activated by acid sensing ion channels (ASICs), mechanosensitive channels, and TRP channels including TRPV1 stimulate bursts of C-fiber activity, which are relayed to the spinal dorsal horn and is perceived as cramping pain; experimental agents that reduce COX-2 expression or directly inhibit FP signalling reduce uterine contractility and behaviour of animal models, highlighting the fact that the overproduction of PGF2α is not just related to dysmenorrhea, but is a mechanistic requirement of the hypercontractility-ischemia phenotype[58].

3.2 Sensitization of nociceptors and mediators of inflammation

The second, closely interconnected layer of pathophysiology of dysmenorrhea is made up of inflammatory mediators and nociceptor sensitization, and accounts for the fact that some patients will feel much more pain than should be reasonable, given the measurable uterine contractility, and why dysmenorrhea tends to increase in severity over time[59]. Along with the synthesis of prostaglandin, the AA released by phospholipase A2 is metabolized by 5- lipoxygenase (5-LOX), in conjunction with 5-LOX activating protein, to 5-HPETE and subsequently LTA4, a branching point of LTB4 cysteinyl leukotrienes LTC4, LTD4 and LTE4, which functions as the co-driver of nociception in clinical and biochemical studies indicate that menstrual fluid and urine of women with moderate to severe dysmenorrhea include very high levels of LTB4 and LTB4 interacts with BLT1 receptors on peripheral neurons and immune cells to stimulate PKC and MAPK signalling cascades, which phosphorylate and sensitize TRPV1, TRPA1, and voltage gated Na+ channels, raising neuronal excitability and reducing threshold to respond to mechanical and chemical stimuli; neutrophils, which probe the uterine wall and menstrual effluent, are also an effective chemoattractant of neutrophils, which release additional cytokines, proteases and reactive oxygen species that Cysteinyl leukotrienes interact with CysLT1 and CysLT2 receptors on vascular smooth muscle and endothelium to cause strong vasoconstriction, vascular permeability, tissue edema, which worsen ischemia and mechanical compression of nerve endings; they also contribute to neurogenic inflammation by inducing mast cell degranulation and histamine release, bradykinin and NGF could independently sensitise nociceptors and induce nerve sprouting[60]. It is this biochemical conditioning that prepares uterine afferents such that normal or slightly elevated concentrations of PGF2α and PGE2 cause disproportional analgesic responses[61]. Furthermore, neurogenic inflammation is a vicious cycle: activated C-fibers antidromically release CGRP and substance P, which further enhances microvascular permeability, activates mast cells and raises the production of local cytokines, enlarging and expanding the inflammatory process[62]. Functional evidence of such mechanisms has been obtained in therapeutic studies: 5-LOX inhibitors (zileuton), dual COX/5 LOX inhibitors, and leukotriene receptor antagonists (montelukast) have been found to decrease the severity of dysmenorrhea in clinical trials, in some cases even as effective as NSAID, and prostaglandins are the primary drivers[63]. The combination of these data suggests that dysmenorrhea cannot be considered only as the activity of the prostaglandins as the contractile disorder but rather as a complex inflammatory pain syndrome, where leukotrienes, cytokines, neuropeptides and growth factors work cooperatively to promote the nociceptor sensitization, the increase of uterine contractility and the persistence of pain beyond the acute burst of prostaglandins[19].

3.3 Hormonal maladjustment as a predictor of the level of pain

Hormonal dysregulation especially the defect in timing, magnitude, and ratio of estradiol and progesterone are significant determinants of pain intensity in dysmenorrhea,

since it controls the extent of production of prostanoids and leukotrienes as well as the sensitivity of uterine and neural tissues to mediators[57]. In normal state, estradiol up regulates COX-2, PLA2 and some prostanoid receptors priming the endometrium and myometrium to a strong yet temporary of inflammatory event during menstruation, and the progesterone down regulates the NF-κB activation, stabilizes lysosomal membranes and down regulates the COX-2, and 5-LOX expression during mid luteal phase, limiting high level inflammatory activity to the short perimenstrual period[19]. The progesterone exposure is truncated or blunted in anovulatory cycles or luteal phases, or luteal insufficiency, and the fall of progesterone is frequently more acute, with a resultant excess disinhibition of NF-κB, PLA2, COX-2 and 5-LOX at the end of the menstrual cycle; menstrual fluid analyses are consistent with this endocrine situation showing higher PGF2α and PGE2 concentrations and higher PGF2alpha:PGE2 ratios in women with abnormal[64]. The hyperestrogenism and low grade inflammation background by systemic conditions disrupting the hormonal balance, including, but not limited to, obesity, which increases peripheral aromatization and circulating estradiol; PCOS, which is a combination of hyperandrogenism and chronic anovulation and low progesterone, and chronic psychological stress, which changes GnRH pulsatility and HPA axis dysfunction, act in synergy to up regulate COX-2, 5-LOX, and cytokine production in the uterus and ovary[65]. There is epidemiologic research suggesting endocrine disrupting chemicals (phthalates, bisphenols and persistent organic pollutants) are associated with menstrual disruptions and dysmenorrhea, and experimental research has suggested that they can change steroid receptor and downstream inflammatory pathway expression in reproductive tissues, but causal relationships in humans are still required[66]. Functional evidence that the endocrine milieu can greatly reduce pain by modifying the level of endocrine systems in dysmenorrhea is clinically demonstrated by the strong efficacy of hormonal therapies in dysmenorrhea: combined oral contraceptives, progestin only regimens, levonorgestrel intrauterine systems, and GnRH analogues in reducing the intensity of pain, not merely by inhibiting ovulation and thickening the endometrium but also by flattening estradiol peaks, lengthening the period of progesterone new longitudinal imaging and neuroendocrine information indicates that recurrent bouts of high pain menstruation in a pro inflammatory, hormonally unbalanced environment may also mediate central sensitization processes by modulating cortisol rhythms, increasing limbic responsiveness to pain, and destabilizing descending inhibitory pathways, such that hormonal imbalance predetermines not only peripheral generator mechanisms (PGF2 3, leukotrienes, uterine hypercontractility) but also the direction of episodic menstrual pain to persistent centrally amplified pelvic pains[67].

3.4 Clinical manifestation: mild to paralyzing dysmenorrhea

Menstrual pain has a broad range of clinical expressions, ranging between mild cramps that are intolerable annoyance to dysmenorrhea that is debilitating and in certain cases becoming chronic pelvic pain with significant central sensitisation and psychosocial comorbidity[68]. Population based studies have shown that although up to 80-90% of menstruating women have some form of menstrual discomfort, only about 10-20% experience painful menstruation to a level that causes frequent absenteeism at school or work, regular use of painkillers or frequent doctor visits, but the minority of the population has a disproportionate burden on loss of productivity and health care service[69]. On the mild end, women generally possess biochemical and contractile phenotypes in or just slightly above physiological ranges, that is, moderately elevated levels of PGF2, PGE2, normal or slightly elevated uterine contraction amplitude, and preservation of endogenous pain modulation, such that pain does not exceed one or two days of menses, is responsive to NSAIDs, and does not largely impair daily functioning[70]. Moving up to moderate and severe dysmenorrhea, menstrual fluid biomarkers demonstrate increasing levels of prostaglandin and leukotrienes, increasing levels of cytokines, and changing ratios of PGF 2 o 1 to PGE 2, followed by imaging and manometric observations of hypertonic myometrium, regular, high amplitude contractions, and decreased uterine blood flow, which is highly correlated with increased and more intense cramps and systemic symptoms, including nausea, vomiting, diarrhoea, fatigue, and Structural or inflammatory changes that coexist such as submucosal and intramural fibroids, adenomyosis, endometriosis, pelvic inflammatory disease increase pain by mechanically distorting the uterine cavity, augmenting endometrial surface area and therewith, prostaglandin production, breaking the balance of coordinated contractility, and creating a local pro inflammatory and neurotrophic milieu of IL 6, IL 8, TGF b and NGF; NGF levels around fibroids and in end Neuroimaging studies in women with longstanding severe dysmenorrhea reveal evidence of central sensitization grey matter reductions in the prefrontal cortex, anterior cingulate and insula, alterations in resting state connectivity of the default mode and salience networks and are functional reorganization of pain modulatory networks including the periaqueductal grey and thalamus, which correlate with catastrophizing, anxiety, and depression of pain[71]. Persistent C fiber input of uterine nociceptors leads to long term potentiation of dorsal horn synapses by NMDA receptor activation, Ca 2 + dependent activation of CaMKII, PKC, and ERK and increased AMPA receptor trafficking, accompanied by IL 1 0, TNF 1, IL 6, and BDNF release by activated microglia and astrocytes that change chloride homeostasis (via KCC2 down regulation) and turns GABAergic signalling into excitatory signals, and psychologically, severe dysmenorrhea is linked with a several fold increased rate of anxiety, depression, and pain catastrophizing and longitudinal research indicates that there is a two way relationship: pre-existing mood disorders predict future pain intensity, and severe dysmenorrhea predict depression and anxiety[72]. The central and psychosocial adaptations clarify the reason

why, in certain patients, pain underlying the period continues between cycles, generalizes to other parts of the body, and becomes inaccessible to regular NSAIDs and hormonal therapy, thus this is why clinical spectrum of dysmenorrhea requires the consideration of early identification of high risk groups and multimodal management approaches that provide not only response to hypercontractile uterus and excessive production of prostaglandins but also inflammatory signalling, central sensitization and psychiatric well-being[73]. Figure 2 describes all the mechanisms discussed in above sections 3.1,3.2 and 3.3.

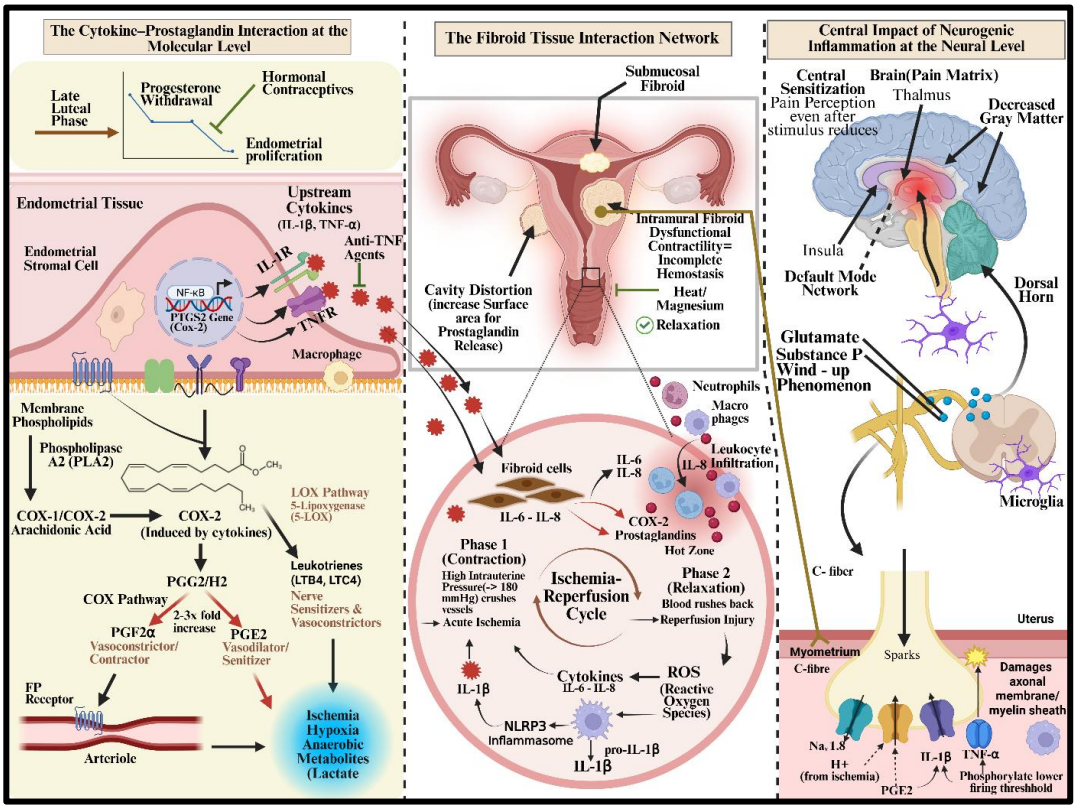

Figure 2: Fibroid-Uterine interaction, cytokine-prostaglandin cascades and neurogenic central sensitization modeling the clinical spectrum of dysmenorrhea.

4. FIBROID DEVELOPMENT AND HORMONAL DRIVERS

4.1 Estrogen and progesterone in the initiation and development of fibroids

The initiation and growth of fibroid is coordinated by estrogen and progesterone via a permissive environment of estrogen progestogen oxidative stress (E–P–OS) network in which a vulnerable group of myometrial stem/progenitor cells is stimulated as a response to chronic steroid exposure, redox disequilibrium, and local paracrine circuits, which augment each other o propose clonal expansion[16]. X-chromosome inactivation and somatic mutation tracing Clonality studies: Individual fibroids are found to be the result of a single transformed smooth muscle or stem like cell, usually with MED12 or HMGA2 mutagens, and then proliferate in response to the mitogenic stimulus of ovarian steroids[1]. Myometrium Fibroid cells upregulate ER and PR (both PRA and PRB) relative to surrounding myometrium and aromatase (CYP19A1) in localised amounts to transform androgens into estradiol in fibroid tissue which reaches intratumoral levels of estrogen several times higher than in systemic circulation especially in obese women where adipose aromatase adds to exposure[74]. ERalpha-mediated activation by estradiol increases expression of progesterone receptor, IGF I and growth factor and prepositions fibroid stem/progenitor cells to respond maximally to luteal phase, but non genomic ER signalling via MAPK/ERK and PI3K/AKT in a few minutes boosts proliferation and survival[16]. Previously regarded as largely protective in the endometrium, progesterone is a direct mitogen in fibroids: it up regulates cell cycle genes (cyclin D1, c MYC), anti-apoptotic molecules (BCL-2, BCL-XL), and ECM genes and down regulates ER the context dependent regulation of ER, and alters the balance towards sustained growth[75]. Human fibroid xenografts in immunodeficient mice are only able to grow when both estradiol and progesterone are present, are quiescent when estradiol is present, and regress when progesterone is antagonized, highlighting the fact that combined steroid signalling (and not estrogen alone) stimulates expansion[76]. These processes are clinically manifested: fibroids are growing during pregnancy and during high-dose estrogen progestin therapy and shrink during menopause or GnRH analogue therapy and change in volume and symptoms responded to selective progesterone receptor modulators (SPRMs) such as ulipristal acetate and vilaprisan with a significant volume change and symptomatic control, but not to pure anti estrogen treatment alone[77]. More recent reports extend this scheme by showing that estrogen and

progesterone also control oxidative stress pathways - enriching ROS generation and weakening antioxidant responses -that stabilizes HIF 1a and augments TGF 8 and activin A expression, which also shows the E- P- OS network is a major factor in hormonal-withdrawal induced fibroid initiation, clonal expansion, and relapse[78]. Figure 3 describes all the mechanisms discussed in above sections 4.1.

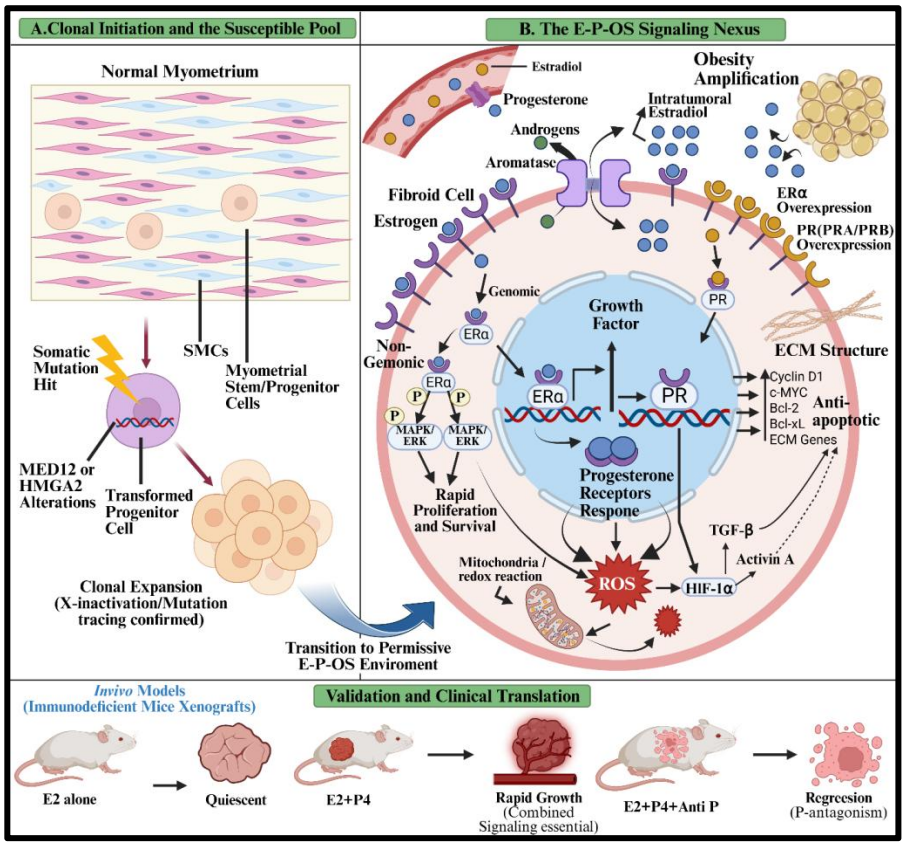

Figure 3. Estrogen progesterone (E 5 2 OS) network in clonal fibroid inception, hormone-regulated growth, and *in vivo* confirmation

4.2 NF-κB signaling, ECM reorganization, angiogenesis

NF-κB signalling, extracellular matrix (ECM) remodelling and angiogenesis are all mutually reliant downstream effectors conveying hormonal and genetic signals to the normal fibrotic, hyper vascular fibroid phenotype[1]. Immunohistochemical and transcriptomic evidence indicates that NF κB p65 nuclear localization and that NF-κB target genes (IL 1, IL 6, TNF 6, COX 2, MMPs) are up regulated in fibroid tissue than adjacent myometrium and 2025 data reveal that the NF 65 activation indices showed a positive correlation with fibroid size and vascular density[79]. NF-κB is triggered by a variety of inputs that are of importance to fibroids such as oxidative stress, mechanical strain due to tissue stiffness, progesterone-mediated RANKL signalling in stem/progenitor cells, and paracrine cytokines to form a feed forward inflammatory loop[79]. Simultaneously, progesterone and estrogen stimulate TGF-3, activin A, connective tissue growth factor (CTGF) and other fibrogenic bases, which through SMAD2/3 and p38 MAPK, cause a drastic up-regulation of collagen I/III, fibronectin, vesicant and other ECM proteins, and an inhibition of decorin and other anti-fibrotic proteins; transforming the myometrial ECM to a stiff, densely cross linked type of matrix capable of replacing up to 70 percent of fib The signalling triggered by stiff ECM feeds back on itself to activate integrins (05B1, 0vB3), focal adhesion kinase (FAK) and RhoA/ROCK, which triggers nuclear translocation of YAP/TAZ and further proliferation and TGF 8 expression, thus suggesting that stiffness per se is a growth signal[80]. Angiogenic remodelling is also pathological: fibroids have more and less normal micro-vessel networks, with higher VEGF, bFGF, PDGF, and angiopoietins in fibroid and surrounding myometrium promoting endothelial growth, pericyte recruitment, and vascular rearrangements, which endothelial perfusion indicates is heterogeneous and relatively hypoxic relative to normal myometrium, which is typical of chaotic vasculature[4]. VEGF and bFGF released by fibroid smooth muscle and stromal cells provide an autocrine, paracrine effect via MAPK and PI3K/AKT to promote cell survival and proliferation and experimental inhibition of VEGF signalling induces micro-vessel paucity and fibroid growth in animal models[81]. All these observations suggest that NF κB mediated inflammation and ECM deposition as well as dysregulated angiogenesis are highly integrated modules downstream of hormonal and genetic drivers and that localized clonal lesions are converted into clinically relevant, stiff, highly vascular but hypoxic tumours leading to pain, bleeding and reproductive dysfunction[82]. Figure 4 describes all the mechanisms discussed in above sections 4.2.

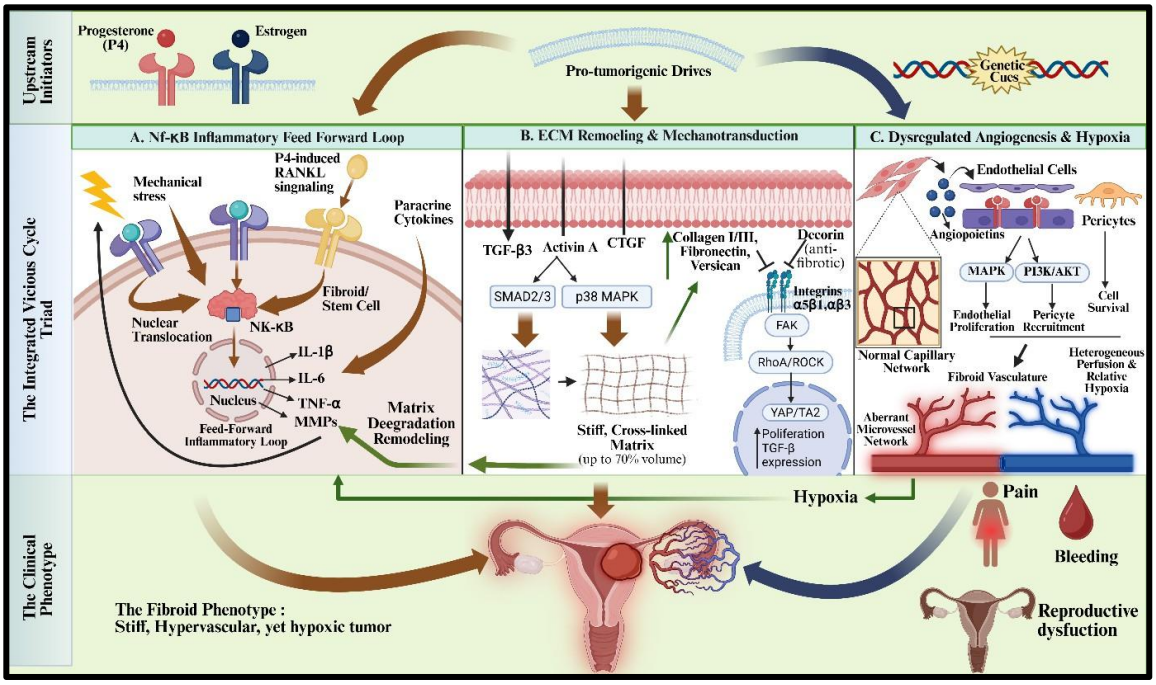

Figure 4. NF-κB-mediated inflammation, ECM remodelling, and abnormal angiogenesis summing up to form the stiff, hyper vascular, hypoxic fibroid phenotype

4.3 Cross talk and dysregulation of hormones (IGF, VEGF, TGF-β)

Growth factor networks are closely embedded with hormonal dysregulation of fibroids with cross talk between estrogen/progesterone, IGF, VEGF, TGF 01, PDGF, and FGF networks controlling cell proliferation, ECM deposition and vascular remodelling. IGF-1R is up regulated by estrogen and progesterone in fibroid cells, IGF signalling through PI3K/AKT and ERK stimulates mitogenesis, inhibits apoptosis, and improves collagen and fibronectin synthesis and phospho-IGF-1R acts as a central mitogenic node given that inhibiting its receptors *in vitro* suppresses fibroid cell multiplication and sensitizes cells to antiproliferative agents[81]. One of the most highly and consistently overexpressed cytokines in fibroids is TGF 3 which interacts with SMAD2/3 to stimulate ECM gene (COL1A1, COL3A1, FN1) expression and inhibit decorin and other proteins involved in matrix regulation, also increasing synthesis of integrins and LOX, reinforcing cross linking and further stiffening of the ECM[83]. PDGF, HGF and EGF supplement this fibrogenic activity and through their proliferation, migration and survival of smooth muscle cells, as well as the expression of MMP and TIMP, remodeling of matrix architecture[84]. The vascular side up regulates VEGF A, VEGF C, bFGF and angiopoietins, with VEGF/VEGFR2 signalling of endothelial proliferation and new vessel sprouting, and bFGF and angiopoietin signalling of nascent vessel stability and pericyte recruitment; ovarian steroids up regulate angiogenic signals with estradiol promoting VEGF and bFGF and progesterone regulating angiogenic receptor expression constituting a hormone dependent angiogenic switch. Notably, these growth factor signaling are not one-way products of hormone activity but are involved in reciprocal regulation: TGF 0 b and activin A can regulate ER and PR expression, IGF signalling can regulate steroid receptor co factor recruitment, and VEGF induced hypoxia can regulate aromatase and steroidogenic enzyme expression, itself feeding back into estrogen/progesterone biosynthesis and sensitivity[48]. This cross talk is also maintained by epigenetic modification including altered DNA methylation and histone promoter marks of the promoters of ESR1, PGR, IGF1, and TGFB3, which suggests that the development of fibroids is a well-coordinated hormone-growth factor-epigenetic loop and not just a response to the overall concentrations of these steroids[85]. This systems level viewpoint is why specific interventions at single nodes (e.g., pure anti-estrogens) tend to only give partial responses and the need to combine interventions that are both able to modulate steroid receptors, TGF-2/SMAD signalling and angiogenic signatures[86]. Figure 5 describes all the mechanisms discussed in above sections 4.3.

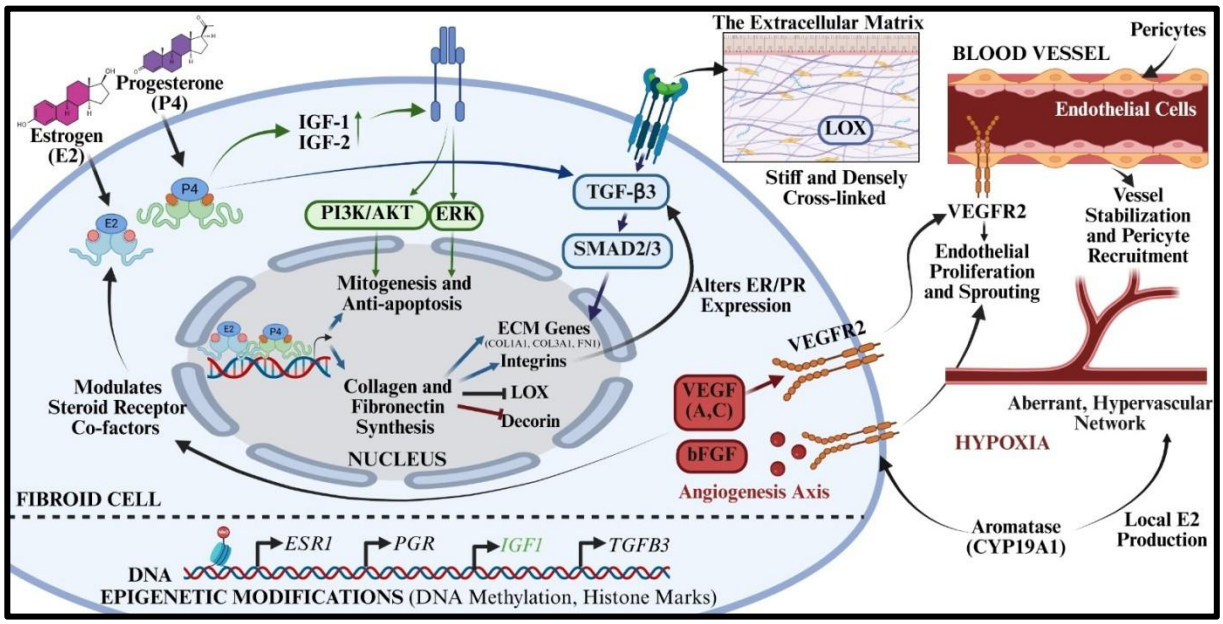

Figure 5. Hormone–Growth Factor Cross Talk (IGF, TGF-β, VEGF) Driving ECM Remodelling and Angiogenesis in Uterine Fibroids

4.4 Fibroids as risk antecedents of ovarian carcinoma

Fibroids per se hardly ever become malignant, the molecular and histopathologic data confirm a sharp division betweenthe benign leiomyoma and leiomyosarcoma, but mounting epidemiologic and mechanistic evidence indicates that fibroids act as an indirect risk factor or indicator of a larger endocrine inflammatory environment that also predisposes epithelial ovarian carcinogenesis[87]. Other studies have found a self-reported or clinically documented history of uterine fibroids to cause a small yet significant elevation in risk of ovarian cancer (adjusted hazard ratios of between 1.3 and 1.6) with stronger results suggesting some histological subtypes and in women who had hysterectomy and not undergone bilateral oophorectomy[88]. Joint exposure 2024-2025 analysis shows that females with the combination of fibroid and hysterectomy have the greatest incidences of ovarian cancer and females with fibroid but no hysterectomy remain at risk with the highest rates based on the timing, amount of the surgery and the hormonal conditions[88]. Mechanistically, fibroids occur in a setting of persistent estrogen progesterone dysregulation, overexpression of aromatase locally, oxidative stress, inactivation of NF 0 KB and overexpression of TGF 0 0 x plus IGFs and VEGF, both also associated with pathogenesis of ovarian tumors and development of pre neoplastic lesions in the fallopian tube and on the ovarian surface epithelium[81]. The presence of chronic pelvic inflammation and altered peritoneal fluid composition in women with fibroids (and potentially coexisting endometriosis or adenomyosis) also has the potential to expose the fimbrial epithelium to cytokines, growth factors, and ROS, which enhance DNA damage and selection pressure in cells already impaired by BRCA or other forms of DNA repair genes[89]. Hysterectomy done to remove fibroids may alter the location and timing of carcinogenesis and may alter ovarian blood supply, hormonal feedback, and tubal anatomy and stroma, although some studies have found that hysterectomy decreases the risk of some subtypes of ovarian cancer by eliminating potential exposures to retrograde carcinogens, whereas other studies have found that hysterectomy is more associated with increased risk in certain subgroups, and initial oophorectomy, though it is clear that the surgical sequelae of hyst Even though leiomyoma to epithelial ovarian carcinoma direct conversion is not substantiated, the perception of fibroids as a clinical expression of protracted steroid hormone excess, growth factor overactivity and pelvic inflammatory stress offers a conceptual context in which to interpret why they coexist with an increased risk of developing ovarian cancer and supports the thesis of your review: that cramps, fibroids and ovarian carcinoma should be viewed as a continuum of hormonal regulation and microenvironmental re-programming, rather than disjointed[88].

5. OVARIAN CARCINOMA DEVELOPMENT

5.1 Hormonal and inflammatory pathways between fibroids and ovarian oncogenesis

The association of fibroids and ovarian oncogenesis can best be considered as a chronic, pelvis-wide (field effect) in which the same endocrine and immune responses that induce benign uterine leiomyomas to progress into malignant ones in the course of decades also signal the fimbrial and ovarian surface epithelia to malignant transformation[90]. The presence of fibroids is related to the context of long-lasting estrogen-progesterone dysregulation: the women with early menarche, nulliparity, obesity, and protracted reproductive lifespan are exposed to a greater lifetime estrogen exposure and are more susceptible to develop leiomyomas, and the expression of genes in fibroid tissue is significantly overexpressing ER alpha and PR, and aromatase (CY19A1) than the surrounding myometrium, indicating that the uterus is becoming a site of autonomous steroidogenesis[41]. This local estrogen excess is no compartmentalized; estradiol

and estrone diffuse in the surrounding myometrium, endometrium and peritoneal fluid, saturating the pelvic organs- fallopian tubes and ovaries - with an estrogen rich environment[91]. Simultaneously, fibroids release pro inflammatory cytokines (IL 1 0 IL 6 TNF 0), chemokines (e.g. CCL2 CXCL8), and growth factors (TGF-0 IGF I/II VEGF PDGF) which leak out a chronic inflammatory/mitogenic signal of the uterus into the wider pelvic cavity[1]. The cyto cytokines and growth factors IL 6, TNF α, and angiogenic factors are increased in peritoneal fluid of women with fibroids and other benign uterine pathologies relative to controls, which is consistent with the previous cytokine and growth factor analysis of ovarian cancer ascites, and which is also consistent with the idea of a common endocrine immune microenvironment in preclinical stages of malignant transformation[92]. This inflammatory-hormonal environment is also enhanced by the common comorbid conditions in women, including obesity, PCOS, and endometriosis, which are enriched in fibroid populations and are themselves hyper-estrogenic and insulin and IGF axis activated and chronic low grade inflammatory and oxidative stress environments[93]. Obesity enhances adipose tissue peripheral aromatase activity, elevating systemic estrogen and exposing the uterus and ovaries to more local steroid (PCOS) and in endometriosis, a cytokine rich, haemorrhagic, peritoneal environment (high IL 1b, IL 6, TNF a, prostaglandins, iron-driven ROS) all of which converge on NF-κB, COX-2, and STAT3 signalling networks that enhance proliferation and survival[94]. The repetitive ovulatory injury and repair of the fimbrial epithelium and ovarian surface/inclusion cyst epithelium occurs in this context: every ovulatory cycle entails a breakage of the ovarian surface, exposure to follicular fluid containing hormones and inflammatory mediators, and repair by estrogen and growth factors; in cases where repair takes place in the context of fibroid associated homologous recombination genes excess, cytokines, and oxidative stress, the likelihood of acquiring and maintaining oncogenic mutations[95]. Experimental models indicate that chronic exposure of tubal or ovarian epithelial cells to estrogens, inflammatory cytokines and TGF-0/IGF rich conditioned media enhances proliferation, anchorage independent growth and apoptotic resistance and expression of early transformation markers and mesenchymal phenotype, which is the mechanistic basis to this field cancerization concept[96]. These strands are joined by a fibroids and cancer risk and propose that fibroids should be thought of as a single phenotypic expression of a system wide endotype of estrogen progestogen inflammation which also predisposes to breast, endometrial and ovarian malignancies via the non-histologic pathway of permanently changing the pelvic microenvironment to a pro tumorigenic state[97]. Under the premises of your review, this implies that cramps, fibroids, ovarian carcinoma and uterine leiomyomas should be placed on a single axis of hormonal disequilibrium and microenvironmental reprogramming with uterine leiomyoma serving both as a biomarker and contributor to the long term hormonal and inflammatory disequilibrium that underlies ovarian oncogenesis[87]. Table 1 describes all the mechanisms discussed in above sections 5.1

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Table 1. Common hormonal-inflammatory processes between fibroids and ovarian carcinoma

Biological Axis	In the Uterine Fibroids	In the Ovarian Carcinoma	In the Mechanistic Bridge	Reference
Excess estrogen	Aromatase (CYP19A1) overexpression, ER/PR increased.	ER-mediated proliferation (serous/endometrioid) and their types.	Chronic high-estrogen pelvis micro-environment.	98 74 99
Inflammatory cytokines	↑ IL-1β, IL-6, TNF-α, CCL2, CXCL8.	Ascetic and tumor stroma elevation.	Promotion of transformation within the field.	100
Growth factors	TGF-β, IGF-I/II, VEGF, PDGF	Stimulate angiogenesis, invasion, metastasis.	As symbolised by common mitogenic signalling.	74
NF-κB activation	Continuous expression of nuclear p65.	Epithelial ovarian carcinoma Constitutively active.	Persistent tumor promoting inflammatory process.	101
COX-2 prostaglandins	High levels of PGE2, PGF2 alpha last stage.	bad prognosis correlated.	NF-κB-COX-2 positive feedback loop.	100 102
Oxidative stress	E -P-OS network activation.	DNA damage and genomic instability.	ROS-mediated mutagenesis.	16 99

5.2 NF-κB-COX-2-prostaglandin in tumor promoting inflammation

Next stage coming in ovarian carcinoma is the NF-κB-COX-2-prostaglandin axis of tumor promoting inflammation[103]. NF-κB-COX-2-prostaglandin axis is a model tumour promoting inflammatory signal that is

active in fibroids and ovarian carcinoma and is presumably active in part of the risk spectrum between benign uterine disease and malignant tubo-ovarian transformation[102]. The immunohistochemical and transcriptomic studies of uterine fibroids show that NF-κB p65 is more highly localized to the nucleus and that it over-expresses its target genes, including IL-1b, IL-6, TNF-α, COX-2 (PTGS2) and a number of MMPs over adjacent myometrium, which suggests that classical NF κB signalling is persistently active in uterine fibroids[100]. NF κB in fibroids can be stimulated by mechanical tension in the ECM, ROS in the E–P–OS network, RANKLRANK signalling in progesterone responsive stem/progenitor cells, and paracrine cytokine loops, after which the NF-κB leads to a pro inflammatory, pro fibrotic program, which promotes proliferation, survival, deposition of ECM, and angiogenesis[41]. NF-κB-induced COX-2 transforms AA to prostanoids, especially PGE2 and PGF2 followed by alterations in fibroids vascularity, which cause heavy menstrual bleeding, dysmenorrhea, and local vascular changes[104]. NF-κB-COX 2 axis is even more closely associated with malignant behaviour in epithelial ovarian cancer: NF κB is constitutively active in most high grade serous and clear cell carcinomas as well as in tumour associated macrophages, and induces expression of anti-apoptotic (BCL-2, BCL-XL, XIAP), cytokine, chemokine, COX-2 and adhesion and invasion genes, and promotes tumour growth, angiogenesis as well as metastasis[105]. COX-2 is up-regulated at both mRNA and protein levels in a high percentage of ovarian tumours and their stroma and high COX-2 expression is associated with elevated FIGO stage, high grade, ascites production, and poor prognosis[106]. Functional experiments indicate that COX-2 overexpression in ovarian cancer cell lines stimulates PGE2 production and wastes proliferation, anti-apoptotic, Matrigel invasion, and metastatic colonization *in vivo*, in large part by mediating the activation of EP2/EP4 targets by cAMP/PKA and PI3K/AKT/ERK signatures and MMP2/MMP9 expression[107]. PGE2 has also been shown to regulate the tumour microenvironment: up regulating VEGF, inducing angiogenesis, and facilitating immune escape: enhancing the expression of PD L1 on tumour and myeloid cells, attracting and expanding regulatory T cells, and polarizing macrophages towards an M2 like, pro tumour phenotype, and inhibiting cytotoxic T cell and NK cell functions[108]. Critically, there is a positive feedback between NF-κB and COX-2 whereby: NF-κB activates COX-2 which can in turn increase NF-κB activation through EP receptor signalling, which maintains chronic inflammation and the generation of prostaglandins[109]. Females that develop fibroids spend years in a condition of hyper-irritated uterine NF-κB activity and COX-2/prostaglandin hyper regulation, as shown by high menstrual and tissue levels of prostaglandins and immunohistochemical NF-κB/COX-2 staining; diffusion of such inflammatory mediators peritoneal and systemic implies that the ovarian epithelium is subjected to a pro inflammatory, prostaglandin rich environment on a lower scale than that observed[110]. It is demonstrated by preclinical studies that NSAIDs, COX-2 selective, and NF-κB pathway antagonists are capable of reducing the tumour burden, angiogenesis, and metastatic spread of tumour in animal models, which is supportive of the notion that this axis is more than a biomarker; it is the driver of tumor promoting inflammation[111]. Accordingly, in our theory of cramps to carcinoma, the NF-κB-COX 2 prostaglandin axis will be a constitutive mechanistic structure: it mediates painful menstrual inflammation in dysmenorrhea, maintains fibroid growth and ECM remodelling, and, in the chronically permissive pelvis, will contribute to the inflammatory and immunosuppressive states that facilitate ovarian tumour genesis and progression[105]. Table 2 describes all the mechanisms discussed in above sections 5.2.

Table 2. NF-κB-COX-2 prostaglandin axis across disease continuum

Factor	Dysmenorrhea	Fibroids	Ovarian Carcinoma	Reference
NF-κB	Cyclic menstrual activation	Persistent nuclear activation.	Constitutive activation	112 100 79
COX-2 (PTGS2)	↑ during menses	Overexpressed	High mRNA and protein expression	113
PGE2	Pain mediator	Facilitates vascularity and ECM remodelling.	Stimulates immunogenicity and angiogenesis.	114 115
Immune effects	Local inflammation	Permanent inflammatory condition of the uterine state.	PD-L1 expression, Treg differentiation, M2 polarization of macrophages.	100
Clinical Impact	cramps	Tumor growth & bleeding	Metastasis, poor prognosis.	114

5.3 Mismanaged estrogen metabolic and genomic instability

Genomic instability and dysregulated estrogen metabolism links fibroid associated hormonal excess to the molecular signatures in ovarian carcinogenesis by integrating ER mediated proliferative signalling with progenitinogenic direct genotoxic impacts of reactive estrogen metabolites[116]. At the receptor mediated signalling level, sustained high concentrations of estradiol and estrone, as

observed in women of long reproductive lifespan, obesity and fibroid associated overexpression of aromatase, foster ER 0.5/0.8-dependent transcription of cell cycle progression genes (cyclin D1, c MYC), survival (BCL2 family), angiogenesis (VEGF), and inflammation (COX 2, IL 6), continuing to expand and sustain the population of proliferating cells in estrogen responsive t With every new proliferation, there is growing likelihood of errors in replication and clonal proliferation of cells harbouring driver mutations[117]. In addition to the growth signalling, estrogens are oxidized by CYP1A1 and CYP1B1 to catechol estrogens (2 hydroxy and 4 hydroxy E1/E2) that can be further oxidized to semiquinones and quinones; 4 OH estrogens, in particular, are genotoxic since their quinones generate unstable, depurinating DNA adducts at N3 adenine and N7 guanine, leaving apurinic sites to further be excised by error prone Reactive oxygen species are also generated in the redox cycling of catechol estrogens leading to oxidative damage to DNA, including 8 oxo dG, strand breaks and chromosomal instability[118]. In normal circumstances, the catechol estrogens are methylated by COMT and the remaining are further detoxified by enzymes like NQO1 and GSTs but in this case, polymorphic changes in the activity of COMT or NQO1 with increased CYP1B1 activity and exposure to high levels of estrogen shift the balance to the formation of genotoxic estrogen metabolites and DNA adducts. Any evidence in ovarian cancer tissue has recorded the unbalanced metabolism of estrogen with enhanced catechol and quinone formation, elevated E2/E1 ratios, altered CYP1B1/COMT expression and higher estrogen-DNA adduct versus normal ovarian tissue, implicating such processes in the carcinogenesis[99]. The local uterine aromatase overexpression and systemic hyperestrogenism in women with fibroids provides a chronically elevated estrogen burden that is metabolized throughout the pelvis, such as the fimbrial and ovarian epithelium; the newly defined E–P–OS (estrogen progesterone oxidative stress) network in fibroids demonstrates that estrogen and progesterone promote oxidative stress, and the ROS, in turn, stabilize and increase steroid receptor signalling, to provide a stable environment of hormonal and ox In BRCA1/2/RAD51C/D/and other homologous recombination repair defect carriers, capacity to repair double strand breaks and bulky adduct related lesions is compromised which together with ovulatory trauma and inflammation gives a plausible pathway starting with the imbalance in estrogen metabolism in a fibroid bearing uterus to high grade serous carcinoma developing in the fimbriae or ovarian surface[119]. Although direct quantitative data collection of estrogen-DNA adducts in ovaries of women with fibroids is scant, the extrapolation of the data of breast and endometrial cancers combined with evidence of unbalanced estrogen metabolism in ovarian cancer and of estrogen-ROS cross talk in fibroids supports the thesis of your review that dysregulated estrogen metabolism and genomic instability are major mechanistic relationships between benign hormonal dysregulation and ovarian malignancy, and not phenomena, but rather reactionary[120]. Table 3 describes all the mechanisms discussed in above sections 5.3.

Table 3. Genomic instability and Estrogen metabolism

Pathway Component	Physiological State	Dysregulated State	Consequence	References
CYP1A1 / CYP1B1	Controlled hydroxylation	↑ 4-OH catechol estrogen formation	Genotoxic quinones	99
COMT	Detoxification through methylation.	Reduced activity / polymorphism.	DNA adduct accumulation	118
ROS generation	Balanced redox	Oxidative stress excess	8-oxo-dG, strand breaks	118
Repair of DNA (BRCA1/2, RAD51C/D)	Efficient repair of HR	Defective in mutation carriers	Mutation fixation	121
Estrogen-DNA adducts	Minimal	Increased in the ovarian tissue	Carcinogenesis initiation	99

5.4 Clinical evidence to relate fibroids and risk of ovarian carcinoma

In the recent years, clinical evidence linking fibroids with ovarian carcinoma risk has grown considerably and when combined with earlier evidence points to fibroids as indirect risk factors and phenotypic indicators of an endocrine inflammatory state that consistently, but proportionately increases ovarian cancer risk but not as precursors[90]. Even when the study is considered as prospective cohort, where the analysis of the Sister Study and large population data is conducted, it is reported that women with a history of clinically diagnosed fibroids have elevated incidence rates of ovarian cancer compared to women without fibroids, and the adjusted hazard ratio is usually within the range of 1.3-1.6 despite the need to consider age, race, parity, oral contraceptive use, BMI, and other reproductive factors[90]. Such associations tend to be stronger with certain histologic subtypes, especially serous and endometrioid carcinoma, and again this is consistent with the same hormonal and inflammatory risk factors being shared by the subtypes[122]. A study in American Journal of Epidemiology which involved comprehensive data on hysterectomy and past history of fibroids, came up with both uterine fibroids and hysterectomy to be

independently associated with increased rate of ovarian cancer, and it was established that women with both exposures were at the greatest risk but the effect of uterine hysterectomy was found to be modifying rather than eliminated and in addition, the risk increases with stratification by whether or not they underwent the procedure of hysterectomy as well as by age during which they under part of the subanalytic evidence suggests that hysterectomy, though not oophorectomy can change ovarian blood flow and ovarian hormonal feedback in a way that is conducive to late carcinogenesis of the remaining ovarian tissue, others show that risk diminishment occurs in women whose hysterectomy was combined with salpingectomy, and again, the surgical details are vital in interpreting epidemiologic signals[90]. Mendelian randomization research has supported orthogonally genetic instruments of uterine leiomyoma characteristics, including one which found that genetically predicted fibroid liability positively related with small yet statistically significant risks of numerous malignancies, including ovarian carcinoma, and that these associations are caused by shared determinants through germline[123]. Overlapping genetic architecture of fibroids, endometriosis, and epithelial ovarian cancer was found in a 2025 phenome wide association study of uterine fibroids, with shared susceptibility loci in genes related to estrogen metabolism, Wnt catenin signalling and inflammatory regulation, supporting the notion that these diseases are caused by shared biological substrates, and not by the coincidental co-occurrence of multiple diseases[124]. In a comprehensive review of the literature to date in Clinical and Experimental Obstetrics and Gynecology, cohort, MR, and mechanistic data were synthesised to reveal that although leiomyosarcomas commonly do not develop as an extension of pre-existing fibroids or direct conversion of leiomyoma into ovarian carcinoma, fibroids are components of a larger phenotype of pro estrogenic, pro fibrotic, pro inflammatory, which predisposes to a variety of hormone sensitive malignancies, including ovarian cancer, particularly. About endometriosis and fibroids and premature mortality is that there is a higher overall cancer and cardiovascular mortality in women with fibroids which is what validates that fibroids are not simply harmless nuisances but health warning[125]. This clinical evidence forms the basis of the argument presented in the narrative of your review that cramps and fibroids are not isolated, self-limited problems but early manifestations of a long running hormonal and microenvironmental disorder that with sufficient time and genetic background appropriate genetic background which, with sufficient time and the proper genetic background could progress to ovarian carcinoma; the AI/ML based risk models that incorporates fibroid phenotype, hormonal profiles, genetic data, and inflammatory biomarkers would identify high risk women in this continuum and subject them to customized surveillance, prophylaxis[126]. Table 4 describes all the mechanisms discussed in above sections 5.4.

Table 4: Clinical study designs relationship between uterine fibroids and high risk of ovarian carcinoma.

Type of study	Key Finding	Risk Magnitude	Interpretation	References
Potential cohort	Fibroids and ovarian cancer	HR ~1.3-1.6s	Moderate and regular increase	90
The histologic subtype analysis	It is more serious in serous & endometrioid	Subtype specific	Shared hormonal risk	127
Mendelian randomization	Genetic liability overlaps	Small but significant	Common germline design	128
Hysterectomy studies	Procedural risk modification	Variable	Surgical context matter	88
Phenome-wide association	(estrogen, Wnt, inflammation) shared loci	Significant overlap	Usual biological substrate	129

6. THE STATED THERAPEUTIC LANDSCAPE

6.1 1NSAIDs, hormonal contraceptives and GnRH modulators

The current medical management of dysmenorrhea and fibroid related symptoms is based on NSAIDs, hormonal contraceptives, and GnRH modulators, yet the effect is rather palliative and symptom based as opposed to disease or cancer prevention[130]. Primary dysmenorrhea is treated with first line NSAIDs since they inhibit COX 1 and COX 2, decrease the production of PGF2alpha and PGE2, overcome hypercontractility of the uterus, ischemic conditions, and nociceptor hypersensitivity, with response rates of 70-80 per cent with first line NSAIDs in primary dysmenorrhea[6]. In the case of fibroid related heavy menstrual bleeding (HMB), NSAIDs show a modest reduction in blood loss (usually 20-30) by reduction of prostaglandin induced vasodilation and platelet inhibition but do not cause fibroid shrinkage or resolution of underlying hormonal causes and are contraindicated by gastrointestinal, renal, and cardiovascular side effects with high chronic dosage[131]. The other major first line class include hormonal contraceptives, which includes combined oral contraceptive pills, progestin only pills, levonorgestrel intrauterine systems (LNG IUS), implants, and injectables[132]. They decrease pain in dysmenorrhea by inhibiting ovulation, stabilizing hormone levels, thinning the endometrium, and decreasing the amount of endometrial arachidonic acid and prostaglandins; continuous or prolonged cycle regimens may be the most effective because they remove menstrual bleeding

completely[133]. LNG IUS: The method is especially useful in fibroid associated HMB of uterine cavities not with large submucosal distortion: it decreases menstrual blood loss by over 80 percent during 6-12 months, enhances hemoglobin, and decreases dysmenorrhea, although with limited effect on fibroid volume and presumably less useful in severely distorted cavities[134]. Combination hormonal therapies may slow down proliferation of fibroid in some cases but may actually stimulate proliferation of fibroid in others, which suggests the complex aspect of the role of progesterone in leiomyoma biology[135]. Second line or pre surgical treatment is with gnRH agonists (e.g., leuprolide) and more recently, oral gnRH antagonists (elagolix, relugolix, linzagolix) with or without add back therapy[136]. These agents reduce LH and FSH, cause hypoestrogenism, and cause fibroid and uterine volume to diminish (usually by 30 to 60 percent), HMB improves, and dysmenorrhea and bulk symptoms improve with randomized trials showing that oral antagonists with low dose add back (estradiol/norethindrone or estradiol/norethisterone) significantly reduce bleeding and fibroid volume, and have an enhanced tolerability compared with agonists[137]. The following limitations are, however, observed in class wide use, such as vasomotor symptoms, bone mineral density loss, mood changes, rebound fibroid growth after discontinuation, which limits their application in short to medium course (typically 624 months) and makes them be definitive long term and prevent cancer measures[138].

6.2 Surgical (myomectomy, hysterectomy, oophorectomy) treatment

A surgical management is still the conclusive treatment in most of the cases of symptomatic fibroids and complex gynaecologic disease in women, and surgical procedures of myomectomy, hysterectomy, and prophylactic or opportunistic oophorectomy have subtle implications in fertility, endocrine fitness, and the risk of long term ovarian cancer[139]. The usual fertility sparing surgery in women with submucosal or large intramural fibroids that cause HMB, dysmenorrhea and infertility or pregnancy loss is myomectomy, done through hysteroscopic, laparoscopic, or open surgery depending on the size, quantity and location of the lesion, and it is necessary to eliminate the tumour, not change the hormonal and microenvironmental conditions that promote new lesion development; recurrence rates are 15-60% over 5-10years, especially in younger women and those Hysterectomy with or without salpingectomy and oophorectomy continues to be the most frequent major gynaecologic operation globally and is the conclusive therapy to fibroid associated symptoms, dysmenorrhea, adenomyosis and abnormal uterine bleeding, but at the cost of uterine activity and, according to age and extent of surgery, may produce psychological, sexual and pelvic floor effects[140]. The association between hysterectomy and risk of developing ovarian cancer remains complicated: some large cohort and case-control studies indicate a modest decrease in ovarian cancer risk in women who have a hysterectomy (hazard ratio is between 0.7 and 0.8), which may be explained by interrupting retrograde carcinogen or endometriosis disease spread and improving the risk of developing salpingectomy, whereas other studies indicatively reveal a higher risk in women who have a hysterectomy and do not have their ovaries removed more than in women Opportunistic salpingectomy at hysterectomy is gaining high recommendations as an act of risk reduction as new data points out that many high grade serous carcinomas begin in the distal fallopian tube and population level modelling indicates that universal adoption may decrease the incidence of ovarian/tubal cancer without the endocrine effects of oophorectomy[141].

In high risk BRCA1/2 carriers, prophylaxis bilateral salpingo oophorectomy (BSO) can reduce the risk of ovarian cancer by 70-90% and breast cancer risk by approximately half when done prior to natural menopause, but in women with average risk, the efficacy of elective BSO at hysterectomy is controversial: it eliminates most of the ovarian cancer risk, but surgical menopause with more cardiovascular-boosting, osteoporotic and cognitive factors cause mortality risks unless It is now recommended by evidence that a normal-risk woman under 50 years should as a rule keep her ovaries in the course of hysterectomy, but that those with high-risk factor scores or genetic score may gain some advantage with BSO; opportunistic salpingectomy is preferable in both groups[142]. Notably, all these surgical solutions such as myomectomy, hysterectomy or oophorectomy do not directly tackle the hormonal and inflammatory milieu within the system that drives the growth of fibroids and ovarian oncogenesis; the surgery only treats the anatomic effect, but not the underlying hormonal and inflammatory drivers, which might still persist in other ovarian tissue, breast as well as other hormone sensitive organs[139].

6.3 Anti-inflammatory and anti-hormonal agents that are targeted

Specific anti-inflammatory and anti-hormonal agents have expanded the therapeutic spectrum beyond the classical NSAIDs and in a broad sense of steroid inhibition, yet they are still concentrated on the symptom control and fibroid volume reduction, but not on explicit cancer prevention[143]. Selective progesterone receptor modulators (SPRMs) like ulipristal acetate became promising disease modifying agents of fibroids: they bind PR with tissue selective agonist / antagonist action, decrease fibroid volume by 30 60, cause amenorrhea in a majority of patients, decrease HMB, and improve quality of life, down regulate PR and ER expression, reduce Ki 67 proliferation indices, and decrease fibrosis of fibroid tissue[144]. Nevertheless, safety issues with rare instances of severe drug caused liver injury caused ulipristal to be suspended or restricted in various areas and new SPRMs are in preclinical tests with a focus on liver safety[145]. Another targeted treatment involves the use of GnRH antagonists together with add back therapy (low dose estradiol and progestin) that demonstrates significant declines in HMB (usually >7080 percent), pain and anemia improvement, and significant fibroid volume reduction (25-50 percent), with add back treatment suppressing bone loss and vasomotor symptoms and allowing them to be used

longer[146]. However, these regimens are still constrained by cost, partial hypoestrogenism and the rebound growth of fibroids following treatment and long term outcome on the risk of ovarian cancers is unclear[147]. Leukotriene pathway inhibitors, and dual COX/5 LOX inhibitors have been considered in the dysmenorrhea space: zileuton and montelukast have shown the ability to reduce the pain in some women and newer agents are proposed to reduce inflammatory nociceptor sensitization with fewer gastrointestinal side effects than NSAIDs but are not yet the standard of care[148]. In the case of endometriosis-related dysmenorrhea, oral GnRH antagonists, aromatase inhibitors, and selective ER modulators are becoming more popular, as well as a move towards more specific hormonal therapy across the gynaecologic diseases[149]. Targeted agents used in ovarian cancer per se are, on the one hand, BRCA/HRD positive tumours treated with PARP inhibitors, on the other hand, anti VEGF (bevacizumab) and immune checkpoint inhibitors, but these agents are mainly applied in advanced malignancy and not in the pre malignant hormonal milieu[150]. Strikingly missing is a group of agents that are specially engineered to normalize the estrogen-progesterone-inflammation network (ER/PR/NF-κB/COX-2/IGF/TGF-β) underlying fibroid biology as well as ovarian oncogenesis. Preclinical studies of nano formulations of curcumin, resveratrol, quercetin, and Nigella sativa derived compounds as phyto-nanotherapies are being investigated as being able to control NF-κB, COX-2, ER signalling, oxidative stress, and angiogenesis simultaneously at lower toxicity than currently available clinical data in fibroid or ovarian cancer prevention[151]. The platforms of AI assisted drug discovery are now starting to find multi target small molecules and phytochemicals, which can theoretically rebalance the hormonal-inflammatory network instead of massively acting on a single receptor, foreshadowing the emergence of the next generation of more mechanistic anti-hormonal/anti-inflammatory therapies that are consistent with the continuum[152].

6.4 Limitations to the prevention of malignant transformation

Although the existing therapeutic measures available to dysmenorrhea and fibroids are diverse that include NSAIDs and hormonal contraceptives, GnRH modulators, SPRMs and surgery, there are considerable limitations to their potential to prevent the emergence of malignant cells, or to have any meaningful impact on reducing the risk of ovarian carcinoma at the population level[153]. The majority of the treatment is focused on the symptom relief (pain, heavy bleeding, pressure) or temporary decrease of the fibroids but not on the redress to the underlying endocrine-immune dysregulation that correlates cramps, leiomyoma, and ovarian oncogenesis[154]. NSAIDs are effective in reducing prostaglandin mediated pain, though to a lesser extent bleeding, but not in normalising estrogen progesterone balance, aromatase overexpression, or chronic NF KB activation; their long term use is limited by systemic toxicity and there is no evidence that NSAID therapy of dysmenorrhea, or fibroids, has any impact on the occurrence of ovarian cancer other than general chemopreventive effects seen in some cohorts of colorectal and breast cancer[155]. There is solid evidence of a protective effect of hormonal contraceptives, especially combined oral contraceptives, which is approximately 30-50% in long-term users, but which is less mediated by specific fibroid-related pathways suppression than by ovulation suppression and decreased lifetime ovulatory cycles; further, COCs may not control fibroid proliferation, and are not used in thrombotic risk women or in women with uncontrolled hypertension[156]. GnRH antagonists and analogues plus or minus additional back can reduce fibroids dramatically and cause amenorrhea, but their hypoestrogenic condition is not long-term, fibroids usually grow again when treatment is stopped, and their effect on cancer risk in the future is unclear[157]. Operative procedures including myomectomy and hysterectomy are definitive solutions to uterine disease and eliminate uterine sources of pain and bleeding, but do not eliminate the underlying systemic hormonal and genetic risk factors that cause ovarian carcinogenesis, and opportunistic salpingectomy and risk reducing BSO can significantly reduce the risk of ovarian cancer in a selected group of women, but is neither necessary nor appropriate in the overwhelming majority of women with benign disease[158]. Notably, the existing therapies do not involve any dynamic risk stratification of the HRD status, inflammatory biomarkers, estrogen metabolite patterns, or AI-based risk scores so that the interventions can be tailored to approach cancer prevention; the management decisions remain very symptom driven, not pathophysiology driven[159]. Also missing are longitudinal studies that relate individual fibroid or dysmenorrhea therapy to ovarian cancer outcomes in the downstream, so it is hard to support the concepts of aggressive prevention of women with average-risk factors[160]. These limitations follow the spirit of one of your review messages; that current therapeutic atmosphere is atomistic and responsive, that the momentarily target cramps and localized disease, and that is comparatively agnostic of the hormonal, inflammatory and genomic continuum with which you relate cramps and fibroids to ovarian carcinoma[126]. This will probably need AI-assisted longitudinal risk modelling, biomarker-mediated intervention timing, and the creation of multi target agents such as rational phytonanotherapeutics, which can restore the estrogen progesterone NF κB COX 2 growth factor network more permanently than individual nodes[161].

7. MACHINE LEARNING AND AI IN GYNAECOLOGY AND ONCOLOGY

7.1 Ovarian carcinoma early imaging and multi-omics AI/ML detection

Early detection of ovarian carcinoma though AI/ML of imaging and multi omics[162]. It is hoped that, by taking advantage of high dimensional patterns that are visible and readable by machines but not by human eyes or single marker assays, AI/ML will be used to detect ovarian carcinoma at an earlier age, before it progresses into its late, symptomatic stages[163]. Existing experience models Deep learning on ultrasound, CT and MRI already

compete at the highest level with expert radiologists in the recognition of benign and malignant adnexal masses, with CNNs trained on massive multi-center ultrasound data already performing well in the 8090 range of sensitivities and specificities and makes malignancy predictions now capable of supporting real time clinical practice. CT radiomics pipelines and multi parametric MRI radiomics pipelines identify hundreds of quantitative features using CT and multi parametric MRI, respectively, and classify them using SVMs, random forests, or gradient boosting models to differentiate benign cysts, borderline tumours, and carcinomas, diffusion weighted and contrast enhanced MRI derive models with AUCs of about 0.83 0.89 and when predicting along with clinical data can match senior radiologists and provide interpretable risks maps[164]. The further augmentation of the architectures with U Net like and transformer yields even better segmentation and volumetry (Dice ≈0.86–0.9) for automatic quantification of the tumour burden and robust longitudinal tracking[165]. Since radiomics provides heterogeneity, perfusion and diffusion restriction that reflects fibrosis, necrosis and angiogenesis, these models act as non-invasive biopsies of a condition image of hormone and inflammation of a conditioned field of a pelvis, as opposed to shape detectors[166]. Besides imaging, multi-omics ML models have been applied to establish molecular subtypes, progression patterns, and survival, platinum sensitivity, and PARP inhibitor sensitivity and immune focused models have defined hot and cold tumours using NF-κB/cytotokine profiles and T cell infiltration, respectively[167]. Radiogenomic Inspirations Predicts BRCA/HRD status systematically with alone imaging studies and predicts longitudinal radiomics (RNNs, survival forests) which learn serial markers (CA 125, HE4), imaging and clinical data in high risk women enable dynamic risk monitoring[168]. Though not yet made routinely available, the variables of fibroid type, vascularity, stiffness and pain (or hormone profiles) can be added a covariate; extending early detection models further along the hormone dysregulation spectrum[169].

7.2 Fibroid progression and severity of pain predictors

AI/ML predictive models of fibroid development and pain intensity can help transform reactive treatment of symptoms to proactive and path based management that is consistent with long term risk[170]. Traditional stratification models using age, race, parity and baseline fibroid size explain only a subset of growth, bleeding and pain variability, whereas ML models which are trained on large datasets of health examination (age, BMI, blood pressure, metabolic features, reproductive history) have achieved an AUC of about 0.8 in predicting risk of fibroid and yield individualised risk scores which can be interpreted in terms of contributions of individual features[170]. Quantitative T1/T2, diffusion, perfusion and elastography (MRI) radiomics based models have shown that they can distinguish between rapidly growing and quiescent fibroids and provide evidence that stiffness and vascular signatures serve as imaging surrogates of TGF 8 -mediated ECM remodelling and angiogenesis[171]. Supervised learning is applied in the initial AI randomised controlled clinical trial studies on dysmenorrhea and chronic pain in the pelvis on symptom diaries, analgesics use, menstrual attributes, comorbidities, and psychological lexicons to discriminate between self-limited pain and progression to chronic pelvic pain and central sensitisation[6]. Such strategies can be reinforced by incorporating hormonal and inflammatory biomarkers and uterine imaging phenotypes, and by training temporal models (RNNs, temporal boosting) on how variations in patterns of hormone variation and uterine contractility within a cycle at the transition between mild and severe cramps or between cyclic and unremitting pain[172]. The idea of an age, fertility goals, fibroid burden, haemoglobin, symptoms, and hormone data combined to recommend medical therapy over myomectomy or hysterectomy and make an approximation of the chances of recurrence demonstrates that ML has direct clinical usefulness[173].

7.3 Drug repurposing and biomarker discovery machine learning

Drug repurposing and biomarker discovery are examples of machine learning to translate an overarching common hormonal and inflammatory pathway into tangible therapeutic and diagnostic applications[174]. Repurposing frameworks integrate interaction of chemical fingerprints, known target-ligand interactions, signature of gene expression perturbation, and pathway information to prioritize approved / investigational drugs that signal GnRH receptor, ER/PR, aromatase, COX 2, PARP, PI3K/AKT/mTOR, AURKB, TGF 0 -interacting biomarkers, and additional TGF 0 -interacting biomarkers related to fibroids and ovarian cancer[175]. Scalable templates of hormone and inflammation repurposing The QSAR + docking + molecular dynamics models have already been applied to identify new GnRH1R modulators and AURKB active compounds. ML driven screens, with repeated hits with statins, metformin, beta blockers, and NSAIDs as adjuncts in ovarian cancer, and supervised multi-omic models show the use of gene and protein panels that predict platinum and PARP response, early detection and risk stratification better than CA 125 and HE4[176]. They are also reduced in terms of feature selection and clustering procedures to generate small, biologically relevant biomarkers sets and show subtypes with distinctive hormone and inflammation patterns[177]. Likewise approaches to fibroid transcriptomes and methylomes reveal ECM, TGF 3 /SMAD, and steroid co regulator modules which segregate molecular subtypes and patterns of growth and prefigures biomarker mediated mechanism based selection of therapy[178]. Integrations of estrogen metabolites, cytokines, eicosanoids, and menstrual effluent small RNAs with ML classifiers can be used to further define at what point benign hormonal perturbation has progressed to pre neoplastic field state[179].

7.4 Computation network modeling, hormonal pathways and inflammatory pathway models

Computational network models of hormonal and inflammatory pathways give a systems level model to relate cramps, fibroids, and ovarian carcinoma as the dynamical regimes of a single regulatory system, and take

interventions *in silico*. Some of the essential sub networks are the HPO axis, local steroidogenesis, ER/PR signalling, NF κB/COX 2/prostaglandin and cytokine cascades, TGF β/IGF/VEGF growth factor signalling, ECM mechanotransduction, oxidative stress, and DNA damage response. These may be modeled as directed graphs, ODE based, Boolean or fuzzy logic models to emulate how various hormonal phenotypes (e.g. early menarche, anovulation, obesity related hyperestrogenism) change the system to a high-ECM, high-NF -state of high risk carcinogenic state[81]. Network models of ovarian cancer define hubs and bottlenecks that include NF-κB, COX-2, BRCA1/2 and PARP whose changes best interfere with tumour promoting circuits[105]. ML is useful alongside the above models, but it is capable of learning edges, parameters with data on cohort scales (Bayesian networks, graphical lasso) and learning time dynamics and between cycles or treatments (dynamic Bayesian networks, RNNs)[180]. Combining longitudinal hormone and cytokine assessment, prostaglandins, radiomics and pain readings can realize the latent conditions that are associated with physiologic menstruation, hyper inflammatory dysmenorrhea, fibroid dominated pathology, and pre neoplastic ovarian fields, and transition probabilities obeying certain exposures[181]. The identification of multi target combinations predicted to change the system to lower risk states is then guided by network medicine concepts and optimisation of drug, dose, and schedule combinations is facilitated by AI driven techniques[182]. This network mapping of phytochemical targets can be used to assess the extent to which candidate nano formulations will cover the vital hubs and feedback loops prior to *in vivo* studies positioning computational network modeling as the mechanistic focus of designing AI directed, multi target, including phytonanotherapeutic strategies to stabilise the reproductive axis in low risk settings[183].

8. PHYTONANOTHERAPEUTICS: NATURAL COMPOUNDS MEET NANOTECHNOLOGY

8.1 Anti-inflammatory and anti-hormonal botanical bioactive (Curcumin, Resveratrol, Quercetin, Green tea polyphenols)

Curcumin, resveratrol, quercetin and green tea polyphenols derived out of plants are at the intersection of inflammation and hormone signalling and hence fully analogous to pains fibroids carcinoma continuum[184]. Curcumin is a potent anti-oxidant and anti-inflammatory agent that inhibits NF-κB, down regulates COX-2 and anti-apoptotic Bcl-2 proteins, attenuates leiomyoma cell viability, and causes apoptosis, with the capacity to suppress Estrogen-progesterone-NF-κB-TGF-β axis to promote fibroid growth and ECM deposition[185]. The grape-derived stilbene resveratrol, too, suppresses fibroid proliferation and ECM accumulation through a decreased expression of collagen and fibronectin and inhibition of TGF-β/SMAD signalling, and explant evidence also indicates actual anti fibrotic and pro apoptotic activity[186]. A prolific source of onions and various ethnomedicinal anti fibroid herbs, quercetin has widespread antioxidant and anti-inflammatory properties and can prevent leiomyoma proliferation and migration by down regulating the genes of ECM, ER, IGF-1, and VEGF signalling, which attaches directly to mechano-transduction and angiogenic modules[187]. Growth, collagen synthesis, and angiogenesis of the fibroid cells through catechins of green tea, especially EGCG are suppressed by modulating the oxidative stress, TGF-β and VEGF through various channels, preclinical and limited clinical data in hormone sensitive cancers demonstrates that EGCG decreases burden in breast and ovarian tumours, and response in uterine is tissue specific[188]. These polyphenols have an inhibitory effect on PI3K/AKT, MAPK and STAT3, sensitize cells to platinum and PARP, control ER/PR and aromatase and reorganize immune and stromal elements, across ovarian and endometrial malignancies[189]. They are also associated with systemic hormonal risk, through re-modeling of gut microbiota and estrogen metabolism, reducing 2 glucuronidase activity, reducing enterohepatic estrogen recycling, and possible reducing estrogen6 estrogen7 adduct formation[190]. When together these bioactives have NF kB, COX2, TGF-β, IGF, VEGF, ER/PR and redox pathways making them theoretically ideal to alter the hormonal and inflammatory networks underlying dysmenorrhea, fibroids as well as ovarian oncogenesis but require nanotechnology based delivery due to their poor solubility and bioavailability[186].

8.2 Nanotechnology-based delivery systems for enhanced bioavailability (liposomes, polymeric nanoparticles, phytosomes)

Nanotechnology delivery systems are aimed at overcoming low solubility, instability, rapid metabolism, poor tissue exposure of phytoactives and increasing their concentrations in hormonally and inflammatory in-balance gynaecologic tissues[191]. Liposomes, solid lipid nanoparticles, polymeric nanoparticles (PLGA, PEG PLGA), micelles, nanogels, phytosomes, exosomes or hybrid systems have been shown to enhance aqueous solubility, degradation resilience, circulation and lesion uptake via the EPR effect, and active targeting of surface ligands respectively[192]. Formulations of nano curcumin (liposomal, micellar, polymeric, exosomal, graphene based) invariably have a greater half-life, improved distribution and an enhanced antiproliferative and pro apoptotic effect in cancer models with lower doses, comparable approaches have been applied to gynaecologic indications[193]. To do it, EGCG has been encapsulated into lipid nanoparticles and decorated folate-PLGA or solid lipid nanoparticles to indulge the overexpression of folate receptors on tumour cells, enhance cellular uptake, *in vitro* cytotoxicity and *in vivo* antitumour efficacy over free EGCG[194]. Multitarget polyphenols can achieve higher local concentrations in any inflammatory site or tumour when using these nano-phyto systems to coordinate the regulation of PI3K/AKT, MAPK, NF-κB, apoptotic and angiogenic pathways, which is more effective than free compounds. PLGA or PEG-PLGA nanoparticles carrying curcumin or resveratrol and integrin, VEGFR2, or ECM-functionalised can be targeted to fibroids and peritumoral myometrium, and EGCG-selected nanoparticles to ER positive or folate receptor positive ovarian cancer,

respectively[195]. Liposomes or phytosomes engineered as transvaginal or intrauterine vectors could attain high local exposure of polyphenols with low systemic exposure, blocking the NF-κB-COX-2 prostaglandin signalling and TGF-0 activating ECM secretion[196]. Plant exosome like nanoparticles Edible plants produce plant derived exosomes with the potential to carry phytochemicals and RNAs and provide a natural vesicle system to deliver anti fibrotic and anti-inflammatory cargo to ovaries and uterus[197].

8.3 Synergistic effect on pain management, fibroid regression and ovarian cancer inhibition

The nano delivery of polyphenols demonstrates synergetic effects in pain relief, fibroid regression and ovarian cancer inhibition as it is the multi target activity of polyphenols, which is enhanced in endocrine, immune and ECM networks by nano delivery[195]. In dysmenorrhea and chronic pelvic pain, curcumin, resveratrol, quercetin, and EGCG suppress NF-κB and COX-2, decrease PGF2 0 /QEG2, TNF 0, IL 1 0, IL 6, and iNOS, and the amount of oxidative stress, which reduce hypercontractility of the uterus, ischemia -reperfusion injury, and hyperirritability of the nociceptor, with models of endometriosis demonstrating less les The local maintenance of drugs through nanoparticle encapsulation and feasibility of low systemic doses has created the opportunity to produce nano curcumin or nano EGCG as adjuncts that will lower the doses of NSAIDs and prolonged spikes in prostaglandins without COX toxicity[198]. In fibroid regression, curcumin and resveratrol reduce proliferation, induce apoptosis, alter ER/PR, block TGF 3/SMAD, IGF-1 and VEGF signalling, and quercetin and EGCG further inhibit collagen, MMPs and angiogenesis and soften and devascularize the fibroid microenvironment. nano curcumin, nano resveratrol and nano EGCG inhibit proliferation, induce mitochondrial apoptosis, decrease angiogenesis, and sensitize platinum and other agent models in ovarian cancer through PI3K/AKT, MAPK, NF-κB, STAT3, VEGF, and MMP pathways[199]. Specific folate-decorated nanoparticles (e.g., folate EGCG-PLGA or multi component micelles e.g. sulforaphane + curcumin) have better uptake and tumour suppression compared to free drugs[28]. In theory, a single nano phyto formulation may be used to concurrently reduce the weight of menstrual inflammation, inhibit fibroid growth, and reduce early oncogenic signalling, but this would require a rigorous dosing and safety phase translation due to the variability in metabolism, herb-drug interaction, and requirements[28].

8.4 Design of phytonanotherapeutics-AI drugs

As a hybrid of phytonanotherapeutics and AI directed drug development, this provides a systematic path towards abandoning empirical utilization of the so-called natural agents and rational, multi target treatment focused on inducing changes in every patient hormone-inflammation system[200]. Phytochemical structures, targets and bioactivities can be trained with ML models; in this case, either graph neural networks, multi task neural networks or QSAR based random forests to predict binding and functional modulation over ER/PR, aromatase, NF-κB, COX-2, TGF-β receptors, IGF-1R, VEGFR2, PI3K and redox enzymes with the aim of selecting or optimising phytochemical combinations that would best cover the core of E-P-O-S and NF-κB-COX2-TGF-β core[201]. Network based computations overlap these targets onto disease modules based on omics of fibroid and ovarian cancer, and measure the efficiency of these candidate cocktails in targeting key hubs and feedback loops[202]. More specific AI-directed nanoparticle design AI enables the selection of carrier composition, size, charge and ligands to maximise concentration in target tissue and minimise off target toxicity; a curcumin RGD folate and folate conjugated PLGA nanoparticle has been fine tuned to be optimised to maximise target tissue accumulation and minimise off target toxicity; folate-conjugated RGD vaginal liposomes have been designed to be optimised to enable uterine delivery of anti-inflammatory polyphenols[203]. They may be implemented in clinical practice by stratifying women along cramps-fibroids-carcinoma continuum by AI based risk models which integrate hormones, inflammatory markers, fibroid phenotype, pain, genetics and imaging and then matching them to a tailored nano phyto regimen (e.g., nano curcumin- EGCG in hyper-estrogenic inflammatory phenotypes, resveratrol-quercetin in ECM rich angiogenic phenotypes) using serial biomarkers and imaging[204]. *In silico* Pre-clinical: *in silico* testing Endocrine An endocrine -inflammation network models can be preclinically optimised to nano phyto designs with a view to transitioning the system between the high risk and low risk attractor states, which then is validated by the laboratory[205]. Figure 6 describes all the mechanisms in section 8.1, 8.2, 8.3 and 8.4.

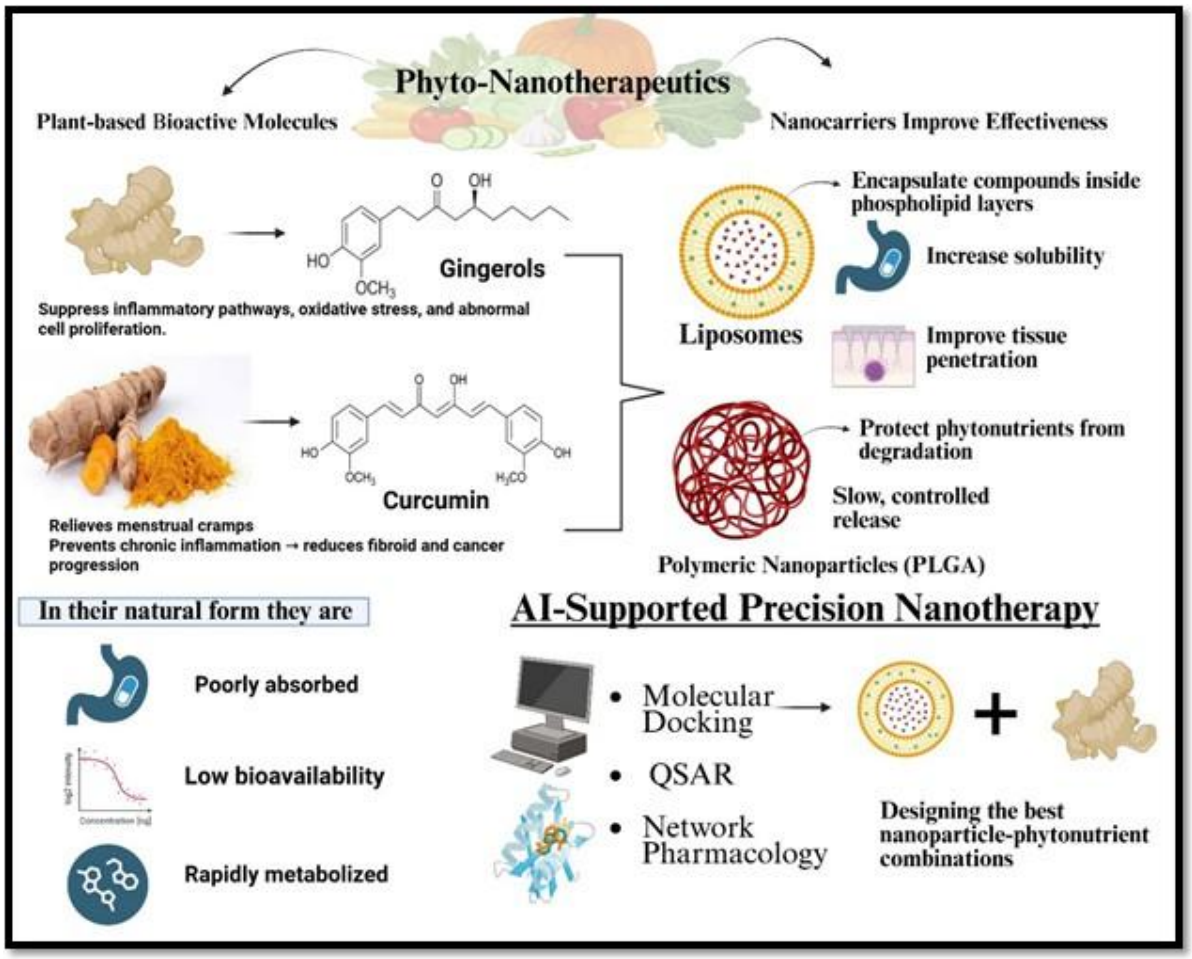

Figure 6: Nanotechnology-enhanced delivery of phytonutrients: Mechanisms, limitations, and AI-supported optimization.

9. PERSPECTIVES OF TRANSLATIONAL AND PRECISION MEDICINE

9.1 Patient stratification based on hormonal, genetic and inflammatory profiles

The stratification of patients based on hormonal, genetic, and inflammatory profiles is important in converting the cramps-fibroids-ovarian carcinoma continuum into a precision medicine model in which the risk, surveillance, and treatment are based on an individual biology and not averages[206]. Use of PARP inhibitors, PI3K/mTOR inhibitors and immunotherapy in gynaecologic oncology is already informed by tumour sequencing, copy number analysis, and immunohistochemistry of identifying BRCA/HRD, PI3K/AKT/mTOR and mismatch repair defects[207]. It is the same reasoning that, when endocrine parameters (age at menarche, cycle pattern, PCOS, obesity, estradiol/progesterone ratios, estrogen metabolite profiles, local aromatase), germline and somatic variants (BRCA1/2, RAD51C/D, MED12/HMGA2, CYP1B1/COMT), and inflammatory markers (CRP, IL 6, TNF α, PGF2alpha/PGE2, leukotriene). In case of fibroids and dysmenorrhea, patient portraits can combine fibroid genotype, fibroid epigenetics, imaging phenotype (number, size, vascularity, stiffness, junctional zone thickness), pain and bleeding scale, and NF 026COX 2cytoprotein signatures[208]. This justifies such clinically meaningful endotypes as hyperestrogenic-hyperinflammatory fibroids, progesterone resistant endometriosis, or low estrogen, high inflammatory dysmenorrhea, each of which has its own risks and the best interventions[209]. These latent subgroups can be discovered with AI assisted risk models and clustering and adaptive basket, umbrella or platform trail designs can provide a test of hormonal, anti -inflammatory and phytonanotherapeutic strategies in biologically defined strata as opposed to histologic categories alone[210].

9.2 The use of AI/ML in conjunction with nanotechnology to create individual algorithms of treatment

The combination of AI/ML and nanotechnology provides an opportunity to map mechanistic understanding of hormonal and inflammatory networks into personalised multi scale interventions[211]. AI is already applied to gynaecologic oncology, where it is used to achieve better diagnostic accuracy, staging, with radiomics and deep learning as well as long combinations of clinical, imaging, and molecular data as well as to make complex decisions[212]. Nanomedicine on the other hand allows delivery of chemotherapeutic, biologic and phytochemicals with greater bioavailability, tumour targeting and reduced toxicity. Connection of these areas means that AI models can take in genomics, hormone and

cytokine data, fibroid molecular subtype, radiomics, pain burden, and comorbidities and prescribe not only endocrine or surgical interventions but the most appropriate designed nano drug regimens including phytonanotherapeutics to each network state of a woman[213]. The design of nanoparticles using ML can be used to optimise composition, size, charge, and ligands in order to tune pharmacokinetics, targeting and toxicity, such as the generation of PLGA nanoparticles co loaded with curcumin and EGCG and functionalised with integrin or folate ligands to target ER/PR positive, ECM rich uterine and ovarian tissue[214]. Clinical decision support systems using AI have the potential to combine changing guidelines and trials to individualise regimens, and radiomics and omics based response models monitor changes in vascularity, stiffness, NF 96B/COX 2 activity, and estrogen metabolite balance, complete the loop between prediction, intervention, and adjustment[215].

9.3 Clinical trial situation of phytonanotherapeutics in gynaecologic al health

Clinical trials of phytonanotherapeutics in gynaecologic health are in their initial phases but have shown promising results, and the best example is green tea polyphenols[216]. EGCG rich green tea extract controlled trial of symptomatic fibroids demonstrated significant changes in fibroid volume and symptom severity with reasonable safety, based on laboratory evidence that EGCG inhibits TGF 2/ SMAD signalling and deposition of ECM[217]. Resveratrol, quercetin and curcumin have extensive preclinical information on fibroids, endometriosis and in reproductive tract and cancer monotherapies have demonstrated benefit in proliferation, fibrosis, angiogenesis and chemosensitivity and few clinical data are available and numerous formulations show varying responses in terms of dosing, endpoint and formulation[186]. Green tea has been most extensively researched in reproductive cancers, where polyphenols target ER/PR, EGFR, VEGF and NF 99B and primitize ovarian and endometrial cancer cells to chemotherapy, but trials are small and usually exploratory[218]. In a wider sense, nano curcumin, nano resveratrol and allied preparations in cancer therapy have shown better bioavailability and biologic efficacy without much consideration in gynaecologic indications[219]. Various botanicals are ethno-pharmacologic review in fibroid symptom and assumed tumour shrinkage but need serious trials using standardized extracts, contemporary imaging and symptoms endpoints and safety evaluation[220]. Virtually no research has yet concurrently used phyto-agents with nanotechnology in gynaecologic disease or implant AI based risk stratification and biomarker selection, making it difficult to ascertain endotype specific benefit. Translational Speed Translation Future basket or platform trials that recruit women with common hormonal-inflammatory phenotypes across fibroids and endometriosis and early neoplasia and randomize them to nano phyto regimens and standard care or the latter alone, using intermediate molecular and radiomic biomarkers, can expedite translation[221].

9.4 Accessibility and ethical issues in health innovations in women

The main challenge to the implementation of precision medicine, AI, and phytonanotherapeutics in female health is ethical and accessibility aspects[222]. Women of affluent, majority groups are overrepresented in high quality genomic, imaging, and clinical datasets, increasing the likelihood that AI generated risk scores and treatment algorithms fail or misclassify women of the Global South, racial and ethnic minorities and lower socioeconomic status[223]. Black box models can be hard to interpret; unreliable deployment can be mistaken, or scarce resources can be allocated in an inappropriate manner. In order to be implemented ethically, it requires numerous types of training and validation cohort, the articulate communication of model uncertainty, and the clinician retention of control. Nanotechnology and phytonanotherapeutics, which may prove expensive, and already patented augment this, which leads to inequity between tertiary centres and the widespread system, although the source botanicals of tertiary centres are inexpensive, encourages, and common in traditional medicine[224]. The chronic exposure of nanoparticles to risk, its interactions with hormonal contraceptives and cancer therapies and its effects in pregnancy and lactation are not fully comprehended and this warrants cautious consent, surveillance and inclusive safety trials[225]. Efficient oncology facilities Advanced oncology facilities, such as molecular boards, sequencing, artificial intelligence, are concentrated in environments with high levels of income; equitable access would necessitate investment in local diagnostics, open source analytics, and policies to allow profiling and targeted treatment to be accessible to the public sector[159]. Ethical issues are also generated by the communication of the cramps–fibroids-carcinoma continuum: the idea of a pre-cancerous body of fibroid bearing women due to the slight increase in risk may become a source of anxiety and overtreatment unless accompanied by the clarity of absolute risk and modifiable factors[226]. In the end, innovations should not only provide state of the art but also ensure that people can access basic analgesia, contraception, minimal invasive surgery and culturally sensitive care[227]. It is vital that equity, community involvement and equitable sharing of benefits (such as in botanical sourcing) be embedded in research and implementation of any of the advanced tools to ensure that they mitigate, and do not exacerbate, global inequality in gynaecologic health[228].

10. FUTURE DIRECTIONS

Menstrual cramps, fibroids and ovarian carcinoma should be integrative and systems level, involving molecular biology, multi omics, AI and nanotechnology-based therapeutics to be as complex as the schema of AI designed, mechano-responsive nanocarrier reestablished uterine mechanical homeostasis. Research must follow the evolution of hormonal dysregulation over the reproductive lifespan including menarche to menopause, and how chronic destabilisation of the estrogen progesterone balance triggers an accelerating pathology with a specific focus on the definition of a molecular transition zone

wherein benign fibroids and chronic inflammation initiate the acquisition of oxidative stress signalling, DNA repair defects, and epigenetic changes prone to carcinogenesis. Both genomics, transcriptomics, proteomics, metabolomics and epigenomics with detailed clinical and imaging data are required to get composite hormonal-inflammatory-genomic signatures that can be used as early biomarkers of dysmenorrhea severity, fibroid presence or progression, and ovarian cancer risk, which can be used to precisely stratify into low and high-risk groups, and be much earlier intervened by. This high dimensional data will be critical to process using AI models, particularly deep learning architectures, to identify pre symptomatic changes in estrogen metabolism, NF κB activation and production of prostaglandins, which are indicators of movement to a high-risk state, and would allow preventive treatments before structural disease is evident. The Endocrine Digital Twins (EDTs) builds on this vision and constructs multiscale virtual avatars of the uterusovary axis that combine longitudinal multi omics with real time measurements of wearable biosensors that detect hormonal changes, inflammatory responses, and pelvic tissue oxygen that can be used to give dynamic biological predictions, signaling when chronic activities of the PGF2alpha-mediated hypercontractility and ECM stiffening are forcing tissue mechanics towards the malignant fibroid phenotype as shown in the diagram. *In silico* testing of phytonanotherapeutics, including nano encapsulated curcumin, resveratrol, or EGCG, of tissue stiffness and gene expression prior to administration could be achieved with mechano-computational twins that explicitly simulate the process of ECM remodelling under cyclical mechanical loading, which would be akin to the step of AI dependent design and optimisation in the figure. Various clinical decision support systems, which are integrated with AI, may then execute thousands of virtual treatment cases on an individual EDT to optimise GnRH antagonists, SPRMs, NSAIDs and nano phyto formulations dosing, and focus the effort of the system progressively on patient-specific primary prevention rather than salvage therapy. The next step in nanomedicine research should be intelligent, mechano-responsive phytonanotechnology that translates the biomechanical activity of uterine hypercontractility and fibroid induced compressive stress and local acidosis in ischemic/hypoxic environments into site specific drug delivery stimuli, which act in response to high stress, low pH microenvironment of the upper panel of the diagram. Self-assembling peptide hydrogels and lipid based nanosensors loaded with a molecular brake e.g. nano EGCG, quercetin or andrographolide could serve dual purpose; rapid analgesia due to COX 2/prostaglandin inhibition as well as more profound disease modification due to PI3K/AKT/mTOR and YAP/TAZ modulation which can normalise ECM homeostasis and tissue stiffness as in the restoration of mechanical homeostasis section. The AI-based molecular dynamics and optimisation should be used to optimise nanoparticle elasticity, size and ligand affinity to align fibroid and malignant ovarian tissue mechanical and receptor landscapes to a maximum efficacy with minimal systemic toxicity and hormonal rebound. At the same time, theranostic nanoplatforms exhibiting an imaging and therapeutic cargo will be useful to monitor fibroid and tumour responses in real time, providing the opportunity to overcome a diagnosis/therapy gap. Nano-phyto priming of epigenetic landscapes is a significant prospect in the future: chronic uterine hypercontractility and oxidative stress presumably induce stable and pathological patterns of the epigenome DNA methylation and histone acetylation, silencing tumour suppressor genes such as p21 and BRCA1; targeted delivery of epigenetically active phytochemicals, including sulforaphane, EGCG, and genistein, by pH responding nanocarriers, could restore this chromatin state to normal to inhibit clonal evolution to car A combination of personalised maps of methylomics of EDTs and these nano phyto primers would enable prophylactic, tissue specific epigenetic reprogramming of high risk women. In all these directions, ethical, societal, and accessibility concerns should be considered at the very beginning: expanding the coverage of trials, creating international data sharing frameworks, and developing cost effective, scalable nanomedicines are necessary to make sure that advanced diagnostics, AI based decision support tools, and phytonanotherapeutics can be available to women of all socioeconomic backgrounds, ultimately allowing women to receive an even more predictive, preventive, and minimally invasive image of gynaecologic care that delivers an earlier diagnosis, more accurate decision support tool, lower recurrence, and recover the quality of life. Figure 7 shows a conceptual framework for one of those possible future directions that combines AI-assisted optimisation with mechano-phytonanotherapeutic nanocarrier systems to improve therapeutic targeting and personalised intervention strategies.

10.1 AI-assisted, mechano-coupled all-mechanical phytonanotherapeutic nano-carrier

Mechano-coupled phytonanotherapeutic nanocarrier could be engineered to react to the stiff, compressed fibroid microenvironment but not solely to biochemical signals. This carrier would remain constant in normal myometrium but would release EGCG/quercetin to high stiffness, strain, acidic pH and hypoxia in fibroid tissue thereby reducing off-target effects. AI would serve as the design engine of this platform by optimizing carrier composition, mechanics and targeting behaviour with *in silico* modelling, molecular dynamics and machine learning. Elasticity and magnetic resonance imaging (MRI)-generated patient-specific uterine digital twins could be then utilized to forecast the effectiveness of the carrier upon entering dense ECM and its discharge of its cargo in a fibroid-like environment. EGCG and other phytochemicals are particularly appropriate as they inhibit fibrotic mediators, suppress the accumulation of ECM as well as regulate YAP/TAZ, AKT and other mechano-inflammatory signalling pathways. When administered via a mechanically controlled nanocarrier, they would assist in ECM softening, inflammation reduction, normalizing tissue stiffness, and restoring uterine homeostasis without a wide-ranging hormonal inhibition.

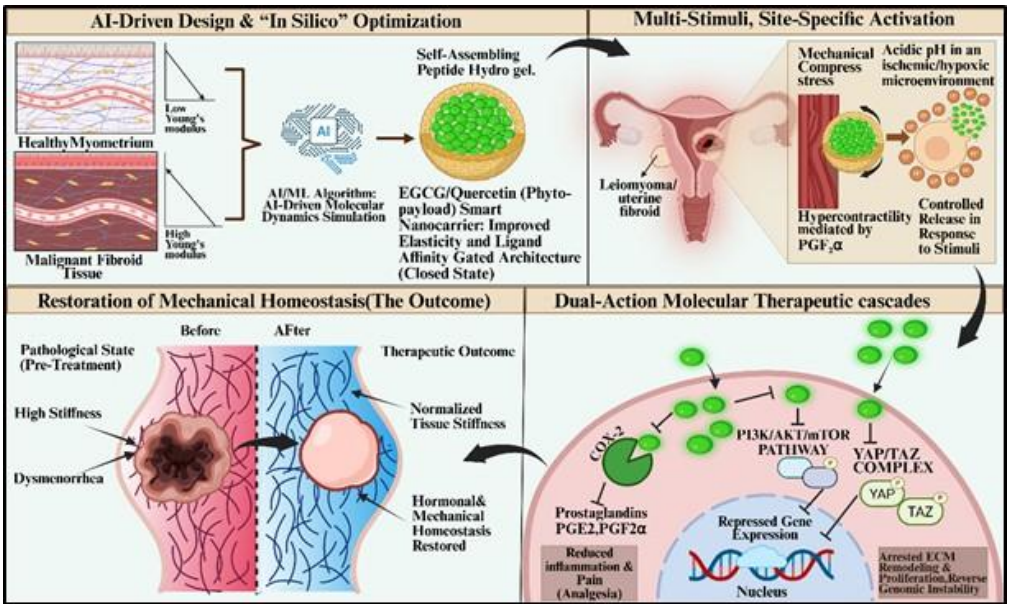

Figure 7: Artificial intelligence assisted, mechano-coupled all-mechanical phytonanotherapeutic nano-carrier to restore uterine mechanical homeostasis and reprogram hormone-inflammation-ECM networks.

11. CONCLUSION

Menstrual cramps, uterine fibroids, and ovarian carcinoma can be considered as the positions on the hormonally, immunologically, and mechanically dysregulated reproductive continuum instead of distinct disorders. Estrogen progesterone imbalance may stimulate inflammatory and fibrotic mediators including NF-κB, COX-2, prostaglandins, cytokines and ECM remodelling resulting in first dysmenorrhea, then fibroid growth, and finally in predisposed women, a tumour permissive microenvironment in ovarian carcinogenesis. Genetic, epigenetic, and mechanotransduction alterations, such as MED12, HMGA2, FH, BRCA1/2, HRD, steroid-metabolism variants, DNA methylation, non-coding RNAs, collagens, integrins, FAK, and YAP/TAZ, further shape this continuum. Treatments currently used are primarily aimed at the management of symptoms or elimination of diseased tissue, although they do not fully restore the underlying endocrine-immune-mechanical network, or are consistent in lowering cancer risk in the long term. Machine learning and artificial intelligence have the potential to transform gynaecology into predictive, personalized care. Radiomics, multi-omics integration, wearable biosensors, and digital twins can assist in the early outcomes of endocrine or inflammatory imbalance, categorize fibroid and tumor biology, and inform early intervention. This can be complemented by nanotechnology, which can be used to deliver drugs or phytonutrients directly to fibroids, inflamed myometrium or ovarian tumors with high spatial resolution. In particular, mechano-responsive phytonanotechnology may deliver agents such as curcumin, quercetin, EGCG, or resveratrol upon detection of stiffness, acidosis, or inflammatory cues, and this would aid in the inhibition of pain, fibrosis, and proliferative signalling. In general, this area is heading towards personalized, preventative gynaecology where severe menstrual pain is addressed as an early warning, fibroids are addressed using predictive and uterum-sparing approach, and the risk of ovarian cancer is tracked before active disease occurs.

LIST OF ABBREVIATIONS

AI/ML	Artificial intelligence and Machine learning
AUC	Area under the curve
BSO	Bilateral salpingo-oophorectomy
CNN	Convolutional neural networks
COX-1/COX-2	Cyclooxygenase-1/2
CRP	C-reactive protein
CT	Computed tomography
ECM	Extracellular matrix
EGCG	Epigallocatechin gallate
EM	Endometrium (contextual)
ER	Estrogen receptor
EPO-S / EPOS	Estrogen-progesterone-oxidative stress network
FAK	Focal adhesion kinase
FH	Fumarate hydratase

FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HIF	Hypoxia-inducible factor
HMB	Heavy menstrual bleeding
HPO	Hypothalamic–pituitary–ovarian axis
HR	Hazard ratio / homologous recombination
HRD	Homologous recombination deficiency
IGF / IGF-1R	Insulin-like growth factor / IGF-1 receptor
IL-6 / IL-8	Interleukin-6 / Interleukin-8
IUS	Intrauterine system
JNK	Jun N-terminal kinase
LH	Luteinizing hormone
LNG-IUS	Levonorgestrel-releasing intra-uterine system
LOX/5-LOX	Lipoxygenase / 5-lipoxygenase
MAPK	Mitogen-activated protein kinase
MED12	Mediator complex subunit 12
MRI	Magnetic resonance imaging
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAIDs	Non-steroidal anti-inflammatory drugs
PARP	Poly(ADP-ribose) polymerase
PCOS	Polycystic ovary syndrome
PGF2-α/PGF2	Prostaglandin F2 alpha
PGE2	Prostaglandin E2
PI3K	Phosphoinositide 3-kinase
PLGA	Poly(lactic-co-glycolic acid)
PR	Progesterone receptor
QSAR	Quantitative structure–activity relationship
RCT	Randomized controlled trials
RGD	Arg-Gly-Asp (tripeptide motif)
RNA	Ribonucleic acid
ROS	Reactive Oxygen Species
SVM	Support Vector machine
SPRM/SPRMs	Selective progesterone receptor modulator(s)
STAT3	Signal transducer and activator of transcription 3
TGF-β	Transforming growth factor-beta
TXA2	Thromboxane A2
VEGF/VEGFR2	Vascular endothelial growth factor / VEGF receptor 2
Wnt	Wingless/Integrated signaling pathway
YAP/TAZ	Yes-associated protein/transcriptional coactivator with PDZ-binding motif

Authors' contributions

Vasundhara Dixit: Data curation, Investigation, Resources, Writing - Original Draft. **Kushagra Gupta:** Data curation, Investigation, Resources, Writing - Original Draft. **Tanya Singh:** Formal analysis, Writing Review & editing. **Ayon Bagh:** Graphic Designing, Referencing. **Neeta Raj Sharma:** Supervision, Writing Review & editing. **Awadhesh Kumar Verma:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing Review & editing, Complete supervision.

Acknowledgment

The authors express their sincere gratitude to the Administration of School of Bioengineering and Biosciences, Lovely Professional University, Punjab, India for providing all kinds of institutional and academic support, along with administrative and technical support from Madinano Global Private Limited, Bihar, India and Navbharat Gurukulam Research Foundation, Bihar, India in carrying out this study.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Yes.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable

Declaration of Competing Interest

The authors state that they have no known financial conflicts of interest or personal connections that could have influenced the work presented in this study.

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