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The role of oestrogen and oestrogen-calcium axis in endometrial carcinoma

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ABSTRACT

Unopposed oestrogen is recognised as an inducer of endometrial cancer. Over the past 50 years, the effects of oestrogen on the endometrium and endometrial cancer have been a hot topic in the field of gynaecological oncology. In recent years, a series of studies by our team revealed that the non-genomic transcriptional effects of oestrogen can influence the progression of endometrial carcinoma by regulating calcium ions, suggesting that inhibiting calcium ion channel proteins could serve as an adjuvant therapy for endometrial cancer. In this review, we retrospectively summarise the sources of oestrogen in vivo, the effects of oestrogens on the uterus and endometrium, oestrogen signalling and the clinical application of oestrogen-related compounds, emphasising the significant role of oestrogen–calcium axis inhibition in adjuvant therapy for endometrial cancer.

INTRODUCTION

Endometrial carcinoma is a significant challenge in the field of women's health and is the most prevalent female reproductive cancer in developed countries.[1] According to Bokhman's pathological histology classification, endometrial carcinoma can be divided into two types. Type I, with a high incidence rate of 65%, is characterised by hyperestrogenism, presenting as anovulatory uterine bleeding, infertility, late onset of menopause, and hyperplasia of the stroma of the ovaries and endometrium.[2] Type II, which has a frequency of 35% and an unfavourable prognosis, and includes serous, clear cell and undifferentiated carcinomas, is not as commonly associated with hyperestrogenism.[3] Patients with type I endometrial carcinoma have 80.2% sensitivity to progestogens, which reduce estrogenic effects. Over the past decades, gynaecologists recognised the hormone oestrogen, a C_{18} steroid, is a double-edged sword—essential for reproductive function yet capable of contributing to oncogenic processes.

Oestrogen is primarily synthesised in the ovaries and adrenal glands. However, due to the presence of aromatase, which is necessary for oestrogen synthesis, small amounts of oestrogen can also be synthesised in peripheral tissues in the brain, bones, breasts and adipose tissue. As a steroid hormone, oestrogen executes its biological effect by binding to estrogen receptors (ERs). In endometrium and endometrial cancer, ERs mainly include classic nuclear ERs, ERα and ERβ, and membrane ERs (eg, G protein-coupled ER, GPER1, also known as GRP30).[4] The different cellular locations of ERs motivate different oestrogen signalling. During the past 10 years, our team has focused on the non-genomic transcriptional effect of oestrogen. Our data showed that oestrogen promotes Ca^{2+} influx from extracellular to intracellular, and in turn regulates cellular proliferation, invasion, differentiation and apoptosis of endometrial cancer cells.[5] Additionally, oestrogen promotes Ca^{2+} channel subunit α 1D (Cav1.3) expression via non-genomic transcriptional effect and increases the migration of endometrial cancer cells.[6] The regulatory effects of oestrogen on Ca^{2+} and calcium channel proteins have led to the application of calcium channel blockers (CCBs) in treating endometrial cancer. In addition, we screened out azelnidipine (AZL), a type of CCB, by a cell proliferation assay, and identified its significant antitumour effect on endometrial cancer.[7] The strategy of regulating oestrogen–calcium homeostasis may serve as an adjuvant therapy for endometrial cancer.

Oestrogen-related compounds have diverse clinical applications in the field of gynaecology and reproductive medicine.[8] Oestrogen analogues, such as estradiol (E_2) and ethinylestradiol, are commonly used in hormone replacement therapy (HRT) to alleviate menopausal symptoms and prevent postmenopausal osteoporosis. These compounds also play a crucial role in contraception and the management of menstrual irregularities. ER modulators, including tamoxifen and raloxifene, have been employed in the treatment and prevention of ER-positive breast cancer, and they exhibit tissue-specific effects on the uterus and endometrium.[9] Additionally, oestrogen inhibitors, such as aromatase

inhibitors (AIs) and selective ER downregulators, have shown promising results in the management of hormone-sensitive breast cancer and endometriosis. Understanding the impact of these compounds on uterine and endometrial physiology is essential for optimising their clinical use and ensuring patient safety and efficacy in gynaecological practice. Further research into the specific mechanisms of action and long-term effects of these compounds on uterine and endometrial health is warranted to advance our understanding of their clinical implications.

In this review, we aim to summarise the diverse sources of oestrogen and dissect its complex effects on the endometrium and endometrial cancer. We will delve into the molecular intricacies of the genomic and non-genomic transcription pathways of oestrogen, elucidating how these signalling mechanisms interact in endometrial cancer. Moreover, we will list the clinical applications of oestrogen-related pharmaceuticals.

A significant focus of our discussion will underscore the importance of the oestrogen–calcium ion channel axis in endometrial cancer adjuvant therapeutics. By elucidating this relationship, we endeavoured to emphasise our series of studies on this subject. This review not only synthesises decades of research but also charts a course for future studies that will further our understanding and refine our approaches to combating endometrial cancer.

OESTROGEN PRODUCTION AND ITS EFFECT ON THE UTERUS

The production of oestrogen, specifically E_2, is commonly associated with the endocrine function of the ovaries. However, it is important to recognise that many other tissues in the body also have the capability to synthesise oestrogens from androgens and to use oestrogen in a paracrine or intracrine manner. In fact, organs such as adipose tissue can significantly contribute to the overall pool of circulating oestrogens.[10] However, whether subcutaneous or visceral fat contributes more to oestrogen levels in endometrial carcinogenesis is controversial.[11 12] Therefore, there is mounting evidence suggesting that in both men and women, the production of C_{18} steroids from C_{19} precursors outside of traditional glandular sites is crucial for normal physiological functions as well as pathological states.

The enzyme aromatase, which is responsible for converting C_{19} steroids to oestrogens, is found in various human tissues including ovarian granulosa cells, placental syncytiotrophoblasts, adipose and skin fibroblasts, bone and the brain. Notably, it catalyses this conversion locally, and its expression in adipose tissue primarily accounts for the extraglandular oestrogen formation. Conversely, excessive or inappropriate aromatase expression has been observed in adipose fibroblasts surrounding breast carcinoma, endometriosis-derived stromal cells and stromal cells in endometrial cancer, resulting in increased local oestrogen concentrations in these tissues.[13] As a result, elevated oestrogen levels promote the hyperplasia of steroid-responsive tissues. Additionally, local oestrogen biosynthesis mediated by aromatase activity in the brain may play a crucial role in regulating various cognitive and hypothalamic functions.[14] The expression of aromatase is under the control of different promoters and transcription factors in various tissues, contributing to tissue-specific and state-specific regulation of oestrogen production (figure 1A). Overall, the process of oestrogen production involving aromatase is intricate and involves a variety of tissues, promoters and regulatory mechanisms, ultimately impacting both normal physiological processes and pathological conditions.

Generally, the causes of hyperestrogenism in vivo are as follows: (1) anovulation, as observed in functional uterine bleeding with anovulatory or luteal insufficiency and prolonged menstrual disorders lacking cyclical changes in the endometrium; (2) obesity, leading to higher oestrogen levels in the blood plasma, which results in progression of the endometrium from hyperplasia to malignancy; (3) polycystic ovary syndrome (PCOS), which lacks regulation of progesterone and periodical shedding, leading to hyperplastic changes in the endometrium (patients with PCOS also exhibit elevated levels of androgens, which can be converted to oestrogen, resulting in endometrial hyperplasia, potentially atypical hyperplasia and even endometrial cancer); (4) ovarian tumours that produce oestrogen, such as granulosa cell tumours and follicular cell tumours.[15]

To study the function of oestrogen in uterus, Meissner *et al* treated diabetic rabbits with stilbestrol and detected nodules formation in both uterine horns.[16] The endometrium was polypoid and poorly demarcated and had microscopic multiple foci of carcinoma (figure 1B). Singh and Bhartiya treated mice pups with E_2 on postnatal days 5–7 and after 7 months; 1 of 60 mice developed uterine cancer. The histological changes show pleomorphic cells containing large, atypical nuclei and multilayered epithelial cells,[17] illustrating that oestrogen can promote uterine cancer (figure 1C). In humans, the risk of developing endometrial cancer in individuals undergoing unopposed oestrogen replacement therapy is three to four times greater than in non-users.[18] The magnitude of this risk is associated with the dosage of oestrogen, particularly prolonged use. For those who have used oestrogen for more than 10 years, the risk of developing endometrial cancer is increased by 18.1 times compared with non-users.[19] Oestrogen can promote endometrial hyperplasia, accelerate cell division and reduce the surveillance function of the immune system against abnormal cells, resulting in the occurrence of endometrial cancer (figure 1D).[20] In the orthotopic implantation model, the researchers implanted the tumour tissue into the uterine horn of mice with or without ovariectomy, and then subcutaneously implanted a release drug delivery system for oestrogen. Tumour growth was observed for 6 weeks (for a total of 8 weeks, including a 2-week tumour implantation period and a 6-week oestrogen stimulation period). All 16 mice with implanted endometrial cancer cells in the uterine horn developed tumours.[21] The study

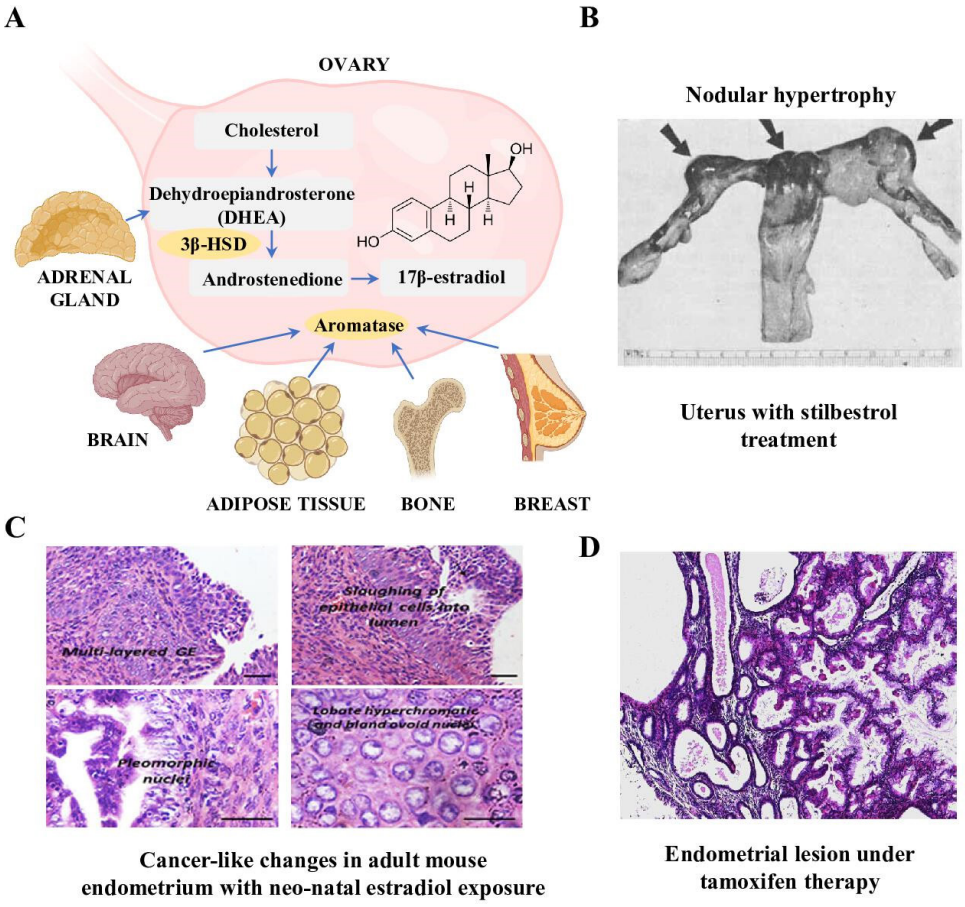

Figure 1 Oestrogen production and its effect on the uterine. (A) The production and catalysis of 17β-estradiol. Dehydroepiandrosterone is formed in both adrenal gland and ovary, whereas aromatase is expressed in ovary, brain, adipose tissue, bone and breast. (B) The uterus of a diabetic rabbit treated with stilbestrol for 10 months showed nodules in both uterine horns and cervices.[16] (C) Histological changes in adult mouse endometrium following neonatal estradiol exposure.[17] Scale: 20 µm. (D) Endometrial lesion after tamoxifen therapy.[20] GE, Gland epithelial cells; 3β-HSD, 3β-hydroxysteroid dehydrogenase.

confirmed that oestrogen promotes endometrial cancer genesis, metastasis and lymphatic infiltration.

THE OESTROGEN PATHWAY IN ENDOMETRIAL CANCER

In hormone-dependent tumours, the oestrogen-mediated mechanism of tumour cell proliferation may involve two pathways: (1) genomic effects (transcriptional effects)—the classic mechanism of oestrogen direct action on nuclear DNA is through the binding of oestrogen to the cell nucleus ER; subsequently, in dimer form, the ER interacts with regulatory regions in oestrogen-responsive genes to initiate downstream gene transcription, promoting cell proliferation; (2) non-genomic transcriptional effects (rapid effects)—oestrogen primarily binds to ER in the cell membrane or cytoplasm, rapidly activating intracellular signal transduction pathways and affecting cell proliferation effects (figure 2).

ER is a glycoprotein with specificity, high affinity and low-binding capacity. Its biological properties are extremely unstable and easily destroyed after being heated. However, the complex formed after binding with the ligand is relatively stable. The natural ligand for ERα and ERβ in vivo is E_2. In the absence of oestrogen, ER binds to heat shock proteins (Hsps) in the cytoplasm and remains in an inactive state. When the ligand binds to the hormone-binding domain of ER, ER undergoes a conformational change and forms a dimer with another ER monomer, leading to Hsp dissociation.[3] The phosphorylated E_2–ER complex is then translocated to the cell nucleus with high affinity for binding to the estrogen response element located in the promoter region of target genes, triggering or inhibiting the assembly of the basic transcription machinery and regulating the transcription of target genes. ERα is also a multifaceted RNA-binding protein and is involved in drug resistance.[22]

ERα and ERβ coregulate oestrogen-responsive genes by cross-talk. Studies have confirmed that the same ligand can mediate different biological activities through ERα and ERβ.[23] The activation domains of the two receptors are different, indicating that they may recruit different proteins to the transcription complex, thereby altering the specificity of genomic transcription effects. Additionally, ER interacts with coactivator proteins to stimulate the activity of other transcription factors such as the AP-1 transcription factor subunit.[24] This cross-signalling between ERα and ERβ allows oestrogen to

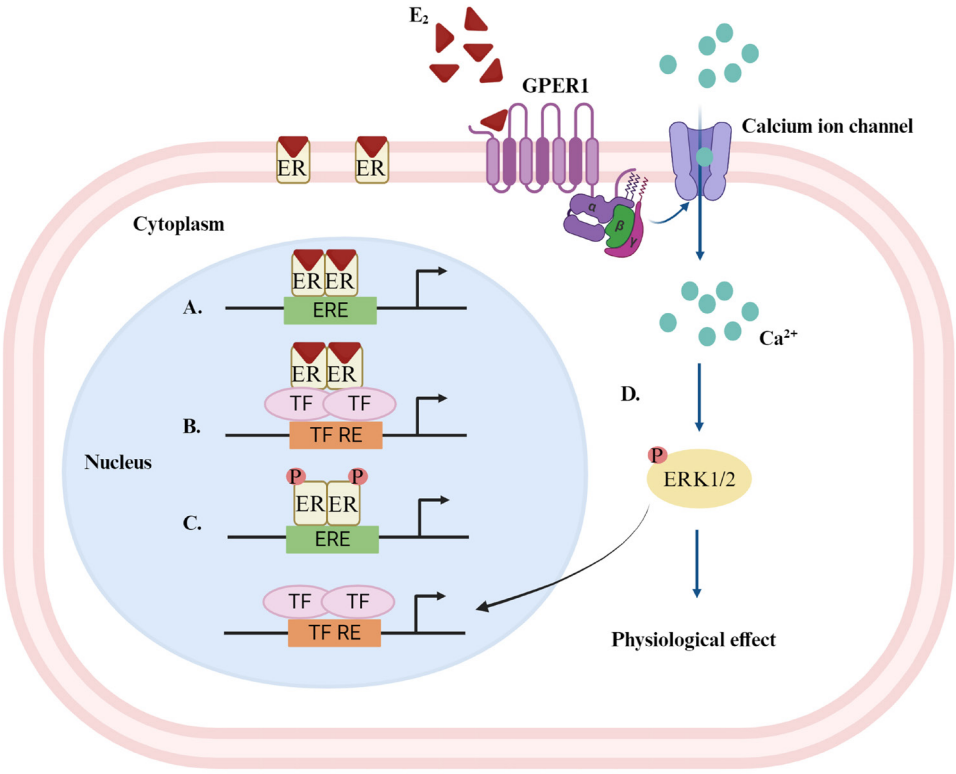

Figure 2 Oestrogen genomic effects and non-genomic transcriptional effects in endometrial cancer. (A–C) Oestrogen genomic effects. Direct genomic effect by binding the E_2–ER complex to the ERE in A, indirect genomic effect by ER–TF interactions in B and ligand-independent effect by ER activation in C. (D) Non-genomic transcriptional effects. E_2-induced rapid calcium changes leading TF responses via protein kinase cascades (created with BioRender.com). E_2, estradiol; ER, estrogen receptor; ERE, estrogen response element; GPER1, G protein-coupled ER 1; P, phosphate group; TF, transcription factor; TF RE, transcription factor response element.

regulate oestrogen-responsive genes at multiple levels in the endometrium.

Oestrogen-mediated non-genomic transcriptional effects have been detected in endometrial epithelial cells, which rapidly activate protein kinase cascades via driving Ca^{2+} influx.[25] Our team found that both oestrogen and its membrane-impermeable conjugate, E_2-conjugated bovine serum albumin, can induce Ca^{2+} influx in the endometrial cancer cell line Ishikawa cells. Oestrogen directly acts on the cell membrane receptor, such as GPER1, to influence the activity of ligand-gated ion channels.[6 26] A high level of albumin-corrected serum calcium is significantly correlated with endometrial cancer progression.[27] We further confirmed that E_2-regulated Ca^{2+} homeostasis in endometrial cancer derives from extracellular Ca^{2+} influx but not the release of the endoplasmic reticulum. In addition to contributing to the activation of protein kinase cascades, E_2-induced Ca^{2+} influx acts on the function of mitochondrial reactive oxygen species and lysosomal activity.[28] Our series of studies provides a new insight into the genesis and progression of oestrogen-induced endometrial cancer, highlighting the role of the oestrogen–calcium axis in endometrial cancer.

OESTROGEN-RELATED COMPOUND

Oestrogen-related compounds include oestrogen itself and oestrogen-related regulators. Oestrogen encompasses natural oestrogen, synthetic oestrogen and phytoestrogen, while oestrogen-related regulator encompasses selective oestrogen receptor modulator, selective tissue estrogenic activity regulator and AI. They have a wide range of clinical applications (figure 3, table 1).

The most common application of oestrogen-related compounds is for menopause hormone therapy (MHT). Menopause is the permanent cessation of the menstrual cycle following a loss of ovarian follicular activity, and most women will spend one-third or more of their lives after menopause. Decreased oestrogen levels during menopause typically result in systemic vasomotor symptoms, including hot flashes and night sweats, anxiety and/or depression, genitourinary atrophy and sexual dysfunction.[29] Postmenopausal oestrogen depletion also has long-term adverse effects, notably bone loss (increased fracture risk) and central abdominal weight gain.[29] MHT can improve menopausal symptoms while preventing menopause-related bone loss and cardiometabolic changes.[9] However, the benefits and risks of MHT remain controversial due to the possible risk of chronic

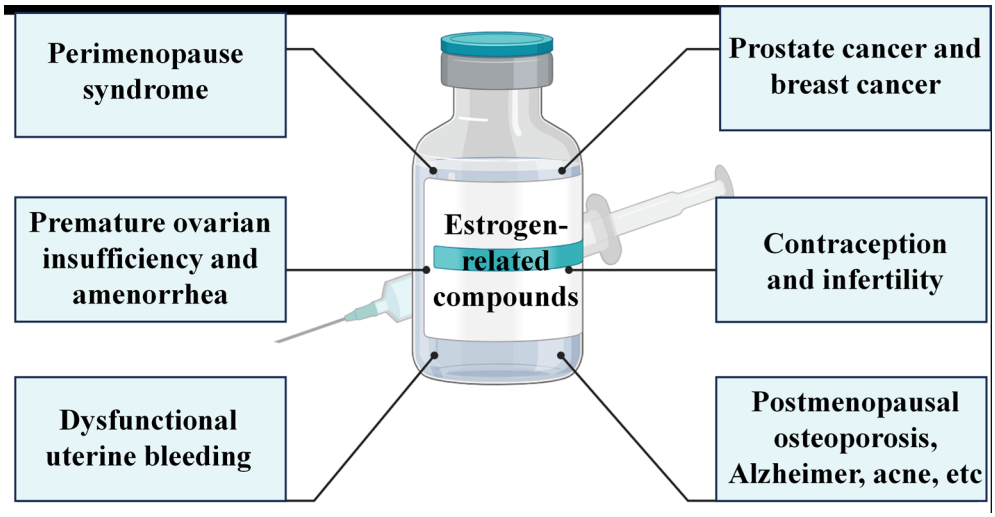

Figure 3 Clinical application of oestrogen-related compounds. Oestrogen-related compounds include oestrogens and oestrogen-related regulators, such as selective oestrogen receptor modulators (SERMs) and selective tissue estrogenic activity regulators. Tamoxifen in the SERM is well-known for being used in the treatment of breast cancer but unfortunately acts as an inducer in endometrial hyperplasia.[50] Subsequently, marketed SERMs were designed to retain agonist effects on bone but act as oestrogen antagonists in the endometrium and breast. The selective estrogen complex (TSEC), a combination of low-dose conjugated oestrogen and the SERM bazedoxifene, was approved in the USA in 2013 and is the newest addition to the combination menopause hormone therapy family.[9] The combination of 0.45 mg of conjugated oestrogen and 20 mg of bazedoxifene in TSEC provides relief from menopausal vasomotor symptoms, improves lumbar spine and total hip bone mineral density, improves sleep and quality of life, and prevents endometrial hyperplasia.[9 51]

diseases such as cardiovascular disease, venous thromboembolism, stroke and dementia.[30]

Natural oestrogens, including 17β-E_2, oestetrol, valproate E_2 and conjugated equine oestrogens are currently recommended as oral oestrogens for the treatment of premenstrual syndrome and perimenopause syndrome. Oestrogen supplementation alone significantly increases the risk of endometrial cancer, so oestrogen alone is used only in women undergoing hysterectomy.[31] Compared with oral administration, transdermal oestrogen bypasses first-pass hepatic effects and therefore may not increase the risk of venous thromboembolism, stroke and gallbladder disease, and is safer at lower doses.[32] Synthetic oestrogen is a natural oestrogen analogue, exhibiting similar functions and potential adverse reactions.

Phytoestrogens are non-steroidal polyphenolic compounds derived from plants with biological properties similar to human oestrogens. Phytoestrogens can be categorised into four groups: flavonoids, coumestans, lignans and stilbenes.[33] Phytoestrogens are present in many dietary supplements and are used as alternatives to synthetic hormones in HRT. In some cases, phytoestrogens, such as phytoestrogen-based HRT, may be more advantageous than other agents and could benefit women suffering from late-onset asthma.[34] A meta-analysis showed a weak negative correlation between increased intake of soy isoflavones and endometrial cancer risk.[35] However, another study reported that high soy isoflavone intake was associated with an increased risk of uterine fibroids in premenopausal women.[36] Additional prospective studies are needed to provide evidence for the clinical use of phytoestrogens.

Tibolone (TIB) is an interesting drug for the treatment of menopausal symptoms that combines estrogenic, androgenic and progestational actions in one compound with different metabolisms in each tissue.[37 38] Following oral administration, TIB is metabolised in the liver to 3α-hydroxy metabolites and 3β-hydroxy metabolites and in peripheral tissues to the Δ^4-isomer.[39] The hydroxy metabolite of TIB has an affinity to bind only to the ER, whereas the Δ^4-isomer has no affinity for the ER but will bind to the progesterone and androgen receptors.[9] In the endometrium, TIB exerts its main progestational effect through the Δ^4-isomer. Therefore, no additional endometrial protection is required for the administration of TIB and cyclic bleeding does not occur.[9] The endometrial safety of TIB has been demonstrated in double-blind randomised controlled trials.[40] In addition, TIB does not cause thrombosis and does not increase the risk of breast cancer.[9 41] Based on these advantages, it is widely used in clinical practice.

AI inhibits the conversion of testosterone to E_2 and androstenedione to estrone (E_1) by inhibiting the rate-limiting enzyme P450 aromatase in the oestrogen biosynthetic pathway. The main AIs currently in clinical use are third-generation AI drugs such as letrozole and anastrozole. AI is the main treatment for ER-positive breast cancer and has also been used to treat conditions such as female infertility and male infertility.[42] A recent clinical study showed encouraging and durable evidence of the activity of letrozole/abemaciclib in recurrent

Table 1 Oestrogen-related compounds commonly used in clinical practice

Categorisation		Drug	Routes of administration	Clinical applications	Effects on the endometrium	Other adverse reactions
Oestrogen	Natural oestrogen	17β-E_2	Oral, transdermal or vaginal administration	Premenstrual syndrome Perimenopause syndrome Osteoporosis Premature ovarian insufficiency Amenorrhoea Dysfunctional uterine bleeding Prostate cancer Postmenopausal advanced breast cancer Alzheimer Acne	Endometrial hyperplasia Endometrial cancer (prolonged unopposed oestrogen exposure)[30]	Gastrointestinal reactions, water and sodium retention, thromboembolism, etc
		Estriol				
		CEE				
	Synthetic oestrogen	Ethinylestradiol	Oral			
		Nilestradiol				
	Phytoestrogen	Isoflavone	Oral	Perimenopause syndrome Obesity Hyperglycaemia Osteoporosis Oxidative stress[52]	No endometrial cancer risk[35] Uterine fibroids in premenopausal women[36]	Suppresses thyroid function (controversial)[53]
Oestrogen-related regulator	SERM	Tamoxifen	Oral	Breast cancer	Weak oestrogen-like effect Endometrial hyperplasia Endometrial cancer[54]	Gastrointestinal reactions, visual disturbances, hair loss, etc
		Bazedoxifene	Oral	Postmenopausal osteoporosis	Oestrogen antagonist Protecting against E_2-induced endometrial hyperplasia[9]	Rarely[55]
	STEAR	Tibolone	Oral	Perimenopause syndrome Vasomotor symptoms (including hot flushes and night sweats) Anxiety and/or depression Urogenital atrophy Osteoporosis Sexual dysfunction	Exerting its progestational effects primarily through the Δ4-isomer[9]	Gastrointestinal reactions, allergic reactions, increasing recurrent breast cancer rates, increasing stroke rates[56]
	AI	Letrozole	Oral	Breast cancer Male infertility Female infertility	Endometrial protection Reducing the risk of recurrent endometrial cancer[43]	Bone and joint pain, muscle pain and fatigue

AI, aromatase inhibitor; CEE, conjugated equine estrogen; E_2, estradiol; SERM, selective estrogen receptor modulator; STEAR, selective tissue estrogenic activity regulator.

ER-positive endometrioid carcinoma.[43] Some reproductive-age patients with endometrial cancer who retain their fertility need to become pregnant through assisted reproduction, but the short-term rise in blood oestrogen caused by ovarian stimulation may lead to the recurrence of endometrial cancer. The use of AI in conjunction with ovarian stimulation may mitigate this risk by reducing serum oestrogen concentrations, as evidenced by an animal study.[44] In a xenograft mouse model, endometrial cancer cells have a growth-promoting effect during ovarian stimulation, and letrozole has an inhibitory effect on the growth of endometrial cancer cells.[44]

In addition, type 1 17β-hydroxysteroid dehydrogenase (17β-HSD-1) is the enzyme that catalyses the final step of oestrogen biosynthesis by reducing the weak oestrogen E_1 to the potent oestrogen E_2. 17β-HSD-1 is overexpressed in endometrial cancer, thus implying that tumours can obtain additional E_2 through this pathway.[45] Whereas oestrogen can promote endometrial cancer progression through multiple pathways, inhibition of 17β-HSD-1 may be a new potential means of treating endometrial cancer. The 17β-HSD-1 inhibitor FP4643 achieved encouraging efficacy in an in situ transplantation model of human endometrial cancer xenografts in mice.[46] FP4643 significantly inhibited tumour growth, metastatic spread and lymphovascular space invasion, with a significant reduction in tumour growth of approximately 65% in the inhibitor group compared with the control group.[46] The study by Konings *et al* also demonstrated the great potential of 17β-HSD-1 inhibitors for the treatment of endometrial cancer.[47] Kaempferol is a common flavonol in the diet, and studies have reported that kaempferol is a potential therapeutic agent for endometrial cancer by inducing apoptosis and inhibiting growth and metastasis via 17β-HSD-1 in endometrial cancer cells.[48]

Furthermore, because of our findings on the role of oestrogen–calcium homeostasis in endometrial cancer genesis and progress, we tried to target calcium homeostasis to treat endometrial cancer. We screened out AZL of 19 Food and Drug Administration-approved CCBs and identified its antitumour effect on endometrial cancer.[7] Liposome-encapsulated AZL was used to form nanoparticles (NP@AZL) for drug delivery, and it exhibited better inhibitory effects on four endometrial cancer cell lines and cells derived from patients with late-stage endometrial cancer. In a mouse model, NP@AZL showed synergistic effects with medroxyprogesterone acetate. This series of studies provides a new approach to the application of antihypertensive CCBs in the prevention and treatment of endometrial cancer.[7]

In conclusion, oestrogen-related compounds have a wide range of applications, such as MHT, adjuvant therapy for oestrogen-related cancers, contraception and assisted reproduction (figure 3, table 1). With the ongoing development of new compounds, comprehensive studies on their molecular mechanisms, clinical efficacy and side effects are needed. Additionally, oestrogen–calcium pathway inhibition is noteworthy adjuvant treatment for endometrial cancer.

SUMMARY

Oestrogen is widely distributed in humans, and disruptions in its synthesis and metabolism can lead to various diseases such as cardiovascular disorders and tumours. The functions of the uterus and endometrium are closely associated with the actions of oestrogen. As an inducer of endometrial cancer, oestrogen plays a crucial role in the development of reproductive function and endometrial hyperplasia.

Oestrogen-induced DNA breakage is an important driver of oncogenesis.[49] Oestrogen-related compounds play a great role in the treatment of diseases, but the risks and benefits are still controversial (especially some compounds increase the risk of oestrogen-related tumour development and recurrence); oestrogen-associated drugs may be able to be modified by materials scientists to perform better. Furthermore, our research has found that oestrogen can enhance the expression of calcium ions and calcium channel proteins in endometrial epithelial cells through non-genomic transcriptional effects, thereby promoting endometrial cancer. We have also explored the auxiliary effects of AZL in the treatment of endometrial cancer,[7] suggesting that calcium channel inhibitors may serve as a means to assist in the treatment of endometrial cancer by counteracting the effects of oestrogen.

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Competing interests JW is the editor-in-chief of *Gynecology and Obstetrics Clinical Medicine*.

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