Hormone Interactions in Endometrial Cancer

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6.1 Introduction

The human endometrium is the main target organ for the ovarian steroidal hormones. The pivotal role of sex hormones in the development, growth and maintenance of the normal physiological structure of the endometrium is well established. Aberrations in the endometrial hormonal milieu due to endogenous or exogenous factors influence endometrial carcinogenesis and cancer progression. Emerging evidence suggests that other non-steroidal hormones are involved in endometrial carcinogenesis via altering the tumour microenvironment and facilitating tumour progression [1]. Understanding the intricate relationship between these hormones in endometrial carcinogenesis could improve the current therapeutic options and lead to the designing of new strategies for the prevention and treatment of endometrial cancer in the era of evolving hormone therapy. This chapter focuses on the influences of both ovarian steroid hormones and the other non-steroidal hormones in endometrial cancer.

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6.2 Hormone Regulators of the Endometrium

Our current understanding of the extensively complex female endocrine system through the well-established hypothalamic-pituitary-ovarian axis of the classical hormone pathway, directed at the endometrium, is far from complete (See Fig. 6.1). The following section provides an overview of the steroidal and non-steroidal hormones that influence the endometrium.

6.2.1 Steroid Hormones

Steroid hormones are cholesterol-derived, lipophilic, small molecular weight compounds characterised by a common cyclopentane-perhydro-phenantrene basic structure. The steroid hormone super family includes sex steroids and corticosteroids [2]. Sex steroids are the main regulators of the endometrium, and are classified according to the number of carbon atoms they contain, progestogens (C21), androgens (C19) and oestrogens (C18). The adrenal glands are also responsible for producing corticosteroids, a small amount of androgens and a relatively large amount of androgen precursors, with the ovaries being the primary site of sex steroid synthesis.

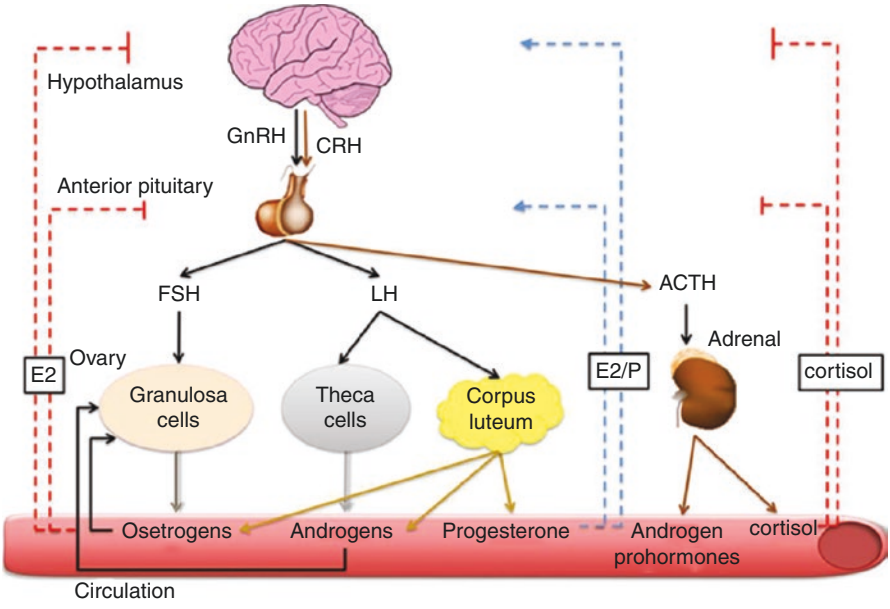

Fig. 6.1 The hypothalamic-pituitary regulation of circulating steroid horemones in premenopausal women. The production of steroid hormones is under the hypothalamo-pituitary regulation; the hypothalamus releases GnRH, which stimulates the release of LH/FSH and corticotrophin releasing hormone (CRH), to signal the ovary and the adrenal glands. Both ovarian estradiol and cortisol in turn have a negative feedback regulatory function at the hypothalamic and pituitary level

Steroid hormones are circulated in blood either as free hormones (less than 3% of the circulating hormones) or bound to proteins. The vast majority of circulatory testosterone and oestradiol are bound to sex-hormone binding globulin (SHBG), whereas cortisol and progesterone are bound to cortisol binding globulin (CBG) with all these hormones also binding to albumin [3]. In women, the sex steroids have a direct, primary effect on the endometrium; the role of corticosteroids and mineralocorticoids on the endometrium is relatively poorly understood.

6.2.1.1 Oestrogens

Oestrogens are the primary "female" sex hormones that regulate endometrial regeneration. In premenopausal non-pregnant women, they are mainly produced by the granulosa cells of the ovary, under the influence of follicle-stimulating hormone (FSH). A smaller amount is produced by extragonadal organs such as the liver, adrenals and fat, which is of a particular importance in postmenopausal women. This chapter focuses on the two major endogenous oestrogens: estradiol (E2), the most potent oestrogen that predominates in the reproductive life, and the weaker estrone (E1) that dominates after the menopause. The least potent oestrogen, the placental-derived estriol (E3), is not discussed further [4].

6.2.1.2 Progesterone

Progesterone produced by the corpus luteum is essential for the endometrial cellular differentiation. It promotes decidualisation, counteracts oestrogen-induced proliferation and, if conception occurs, maintains the pregnancy. Adrenals also produce progesterone, which is largely converted into glucocorticoids and androgens without being released in to the circulation. The half-life of progesterone is as short as 5 min; being either promptly deactivated in the liver or converted in the kidney to a potent mineralocorticoid [5].

6.2.1.3 Androgens

The main circulating forms of androgens in women include the prohormones, dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione and testosterone, which are produced primarily by the adrenals and the ovarian theca cells. The subsequent metabolism of these prohormones in peripheral tissue produces the highly potent androgens, testosterone and dihydrotestosterone (DHT), which have a high affinity to androgen receptors (AR) [6]. In addition to being precursors for oestrogen, the available evidence suggests that androgens, via AR are directly involved in stromal decidualisation in the endometrium [7]. The direct function of androgens in the endometrial epithelial cells, however, is less well characterised.

6.2.1.4 Corticosteroids

Two types of corticosteroids are produced by the adrenal cortex, glucocorticoids (e.g. cortisol, produced by the outermost layer, the zona glomerulosa) and mineralocorticoids (e.g. aldosterone produced by the middle layer, the zona fasciculata). Glucocorticoid production is regulated by physical or emotional stress and pain,

whilst angiotensin II of renal origin, as part of the renin angiotensin aldosterone system, is the main regulator of mineralocorticoid production. The regulation of carbohydrate and protein metabolism by cortisol and the fluid and electrolyte equilibrium by aldosterone have been well recognised. However, direct regulatory effect of these hormones on human endometrium remains to be fully confirmed. Glucocorticoids may regulate endometrial survival, menstruation and parturition via inflammatory and immunological responses [8]. Mineralocorticoid levels vary during the menstrual cycle being highest during the luteal phase and increasing progressively during pregnancy [9, 10].

6.2.2 Non-steroidal Hormones

Many of the endocrine organs including those of the hypothalamo-pituitary axis produce non-steroidal hormones that may have direct, non-classical effects on the endometrium. These hormones are detailed below.

6.2.2.1 Gonadotrophin Releasing Hormone (GnRH)

GnRH is a decapeptide hormone that is secreted in a pulsatile manner (continuous stimulation downregulates the pituitary), and has at least two isoforms. GnRH I is responsible for both follicle stimulating hormone (FSH) and luteinising hormone (LH) secretion from the anterior pituitary [11], whilst GnRH II may play a role in the behavioural components of reproduction. In endometrial cells, GnRH may have a direct effect on proliferation, apoptosis and tissue remodelling [12].

6.2.2.2 LH and FSH

FSH and LH are glycoprotein hormones with synergistic actions on the ovary. In women, FSH signals the synthesis of the steroid hormones oestradiol, progesterone and testosterone maturation of ovarian follicles, whilst LH triggers ovulation and acts on the theca cells to produce androgens. Gonadotrophins are released in a pulsatile manner according to GnRH pulses, with higher FSH levels observed in the mid-follicular phase of the cycle and LH peaking at the mid-cycle, pre-ovulatory phase. This mid-cycle LH surge is thought to be induced by both oestrogens and progesterone [13]. Although the primary gonadotrophin target is the gonads, they also have extra-ovarian actions in other non-classical target organs such as the endometrium [14, 15].

6.2.2.3 Thyroid Hormones

Thyroid hormones (TH) include the active form, triiodothyronine (T3), and the prohormone, thyroxine (T4), which are tyrosine-based peptides, regulated by thyroid stimulating hormone (TSH) of anterior pituitary origin [16]. Approximately 70% of THs are bound to thyroid-binding globulins (TBGs) in plasma, creating a substantial reserve, whereas the free hormone can diffuse across the plasma membrane of target cells. Although circulatory TH levels do not fluctuate substantially during the menstrual cycle [17], the mean thyroid volume increases by 50% in the luteal phase

[18] implying an altered thyroid function. Importantly, deiodinase 2 (DIO2), which converts T4 to the more potent T3, is present in human endometrium. DIO levels undergo cyclic changes in the human endometrium showing an inverse relationship with progesterone levels [19]. This observation may suggest progesterone suppresses the action of circulating thyroid hormones in the endometrium and merits further investigation. Both thyrotoxicosis and hypothyroidism alter gonadotrophin release, circulatory levels of SHBG and steroid metabolism, resulting in a variety of menstrual disorders [20].

6.2.2.4 Insulin

Insulin is a water-soluble polypeptide anabolic hormone produced by beta cells of the pancreatic islets of langerhans. Insulin promotes the uptake and storage of carbohydrate, amino acids and fat into liver, skeletal muscle and adipose tissue and antagonises the catabolism of these fuel reserves. It also has effects on cell growth, cognition and the vasculature, which are separate from its metabolic actions [21].

The half-life of insulin in the circulation is short (2–3 min), and being water soluble, it can travel freely in the blood to exert its effects via a cell membrane receptor. It has been noted that insulin is higher during the luteal phase of the menstrual cycle but the magnitude of change is rather small and not very relevant in interpreting test results [22].

6.2.2.5 Melatonin

Melatonin, or *N*-acetyle-5-methoxy-tryptamine, is a non-steroidal peptide hormone. It is produced by the pineal gland through metabolism of the hormone serotonin [23] and released under hypothalamic regulation. The suprachiasmatic nucleus communicates with the hypothalamus via sympathetic neurons in the spinal cord resulting in diurnal variation. Melatonin is produced maximally at night and thus plays a role in the sleep–wake cycle [24]. Melatonin also acts as an immune modulator, antioxidant and has anti-angiogenic effects with a role in reproduction [25].

Melatonin interferes with oestrogen signalling pathways and inhibits the activity of aromatase, reducing the conversion of androgens to oestrogen [26]. In female rats, removal of the pineal gland and subsequent decrease in circulating melatonin levels result in an increase in oestrogen, decrease in progesterone and reduced number of successful embryo implantations. This effect is reversed on administration of melatonin [27].

6.3 Steroid Hormones Intracrinology of the Endometrium

Intracrinology refers to the local intracellular biosynthesis and metabolism of hormones in peripheral tissues, followed by local inactivation of these hormones with minimal or no alteration of serum levels [28]. The intracrinology process is mediated by two main classes of proteins: the cytochrome P450 proteins and the hydroxysteroid dehydrogenases [29, 30], most of which have already been characterised in the endometrium (See Fig. 6.2). In physiological settings, this process is

Enzyme and gene names

P450scc (cholesterol side chain cleavage)=*CYP11A1*
3βHSD1-3 (3β hydroxysteroid dehydrogenase)=*HSD3B1-3*
3αHSD1-3 (3α hydroxysteroid dehydrogenase)=*HSD3A1-3*
17βHSD1-12 (17β hydroxysteroid dehydrogenase)=*HSD17B1-12*
17,20 lyase (17α hydroxylase)=*CYP17A1*
DHEA sulfotransferase=*SULT2A1*
Aromatase=*CYP19A1*
5α reductase1-3=*SRD5A1-3*
P450-C=*CYP1A1*
P450-1B1=*CYP1B1*
P450-C3=*CYP3A4*
Catechol-O-Methyltransferase=*COMT*
Steroid Sulfatase Isozyme S=*STS*
Glutathione transferases =*GST*

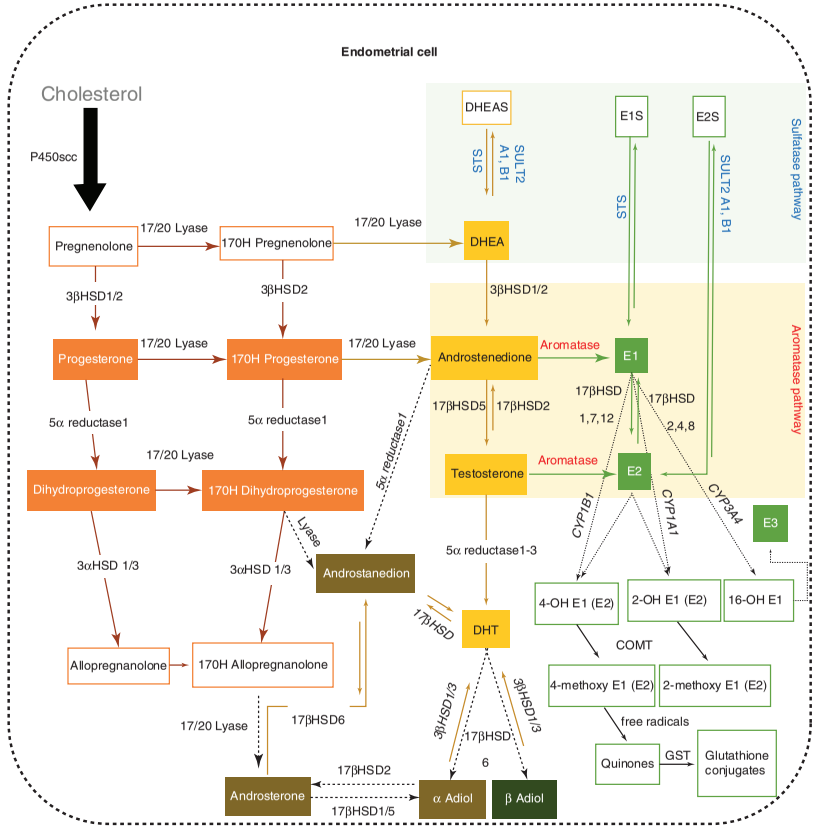

Fig. 6.2 Steroid hormone intracrinology (the local synthesis and metabolism of steroid hormones) in the endometrium. Many enzymes involved in steroid hormone metabolism are expressed in endometrial cells. Active hormones that bind their cognate receptors are in coloured boxes, while those which are inactive or are not a ligand for steroid receptors are in white boxes. Metabolites in black patterned boxes possess steroidal activity and can bind cognate receptors before conjugated to sulphate or glucuronide

essential for fine tuning of the final steroid hormone concentration in the endometrium required for the specific cellular action. An imbalance in the biosynthesis and/or inactivation process of steroid hormones has been described in hormone-dependent tumours such as breast, prostate and endometrial cancers [28] and are expected to play a role in resistance to endocrine therapy. Many different circulating forms of oestrogen, progesterone and androgens occur and they are substrates for the steroid metabolising enzymes expressed in the endometrium.

6.3.1 Progesterone Intracrinology

The general consensus is that the rate-limiting step in progesterone synthesis mediated by steroidogenic acute regulatory protein (STAR) does not take place in intracrine tissues [31]. However, emerging experimental data suggests that endometrium possesses all the enzymes required for *de novo* progesterone synthesis including STAR, P450 side chain cleavage enzyme (CYP11A1) and 3β HSD (See Fig. 6.3) [32]. Endometrial stromal and epithelial cells also express the enzymes that metabolise progesterone into compounds with a low affinity to PR (e.g. 20α-HSDs, 5α-reductases and 3α-HSDs) and progesterone deactivating enzymes [33]. Decreased expression of genes involved in progesterone biosynthesis (STAR and

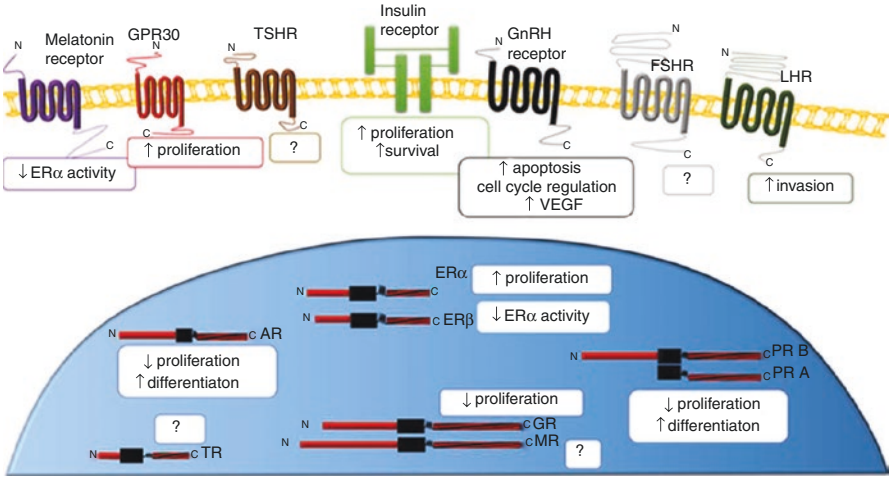

Fig. 6.3 Hormones receptors in endometrial cells. A schematic illustration of the localisation of steroid and non-steroidal hormone receptors and the effects of receptor activation on endometrial cells. Steroid hormone receptors are nuclear and function as ligand-activated transcription factors, whereas non-steroidal receptors are mostly located in the cell membrane. *GPR30* G protein-coupled receptor 30, *TSHR* thyroid stimulating hormone receptor, *GnRH receptor* gonadotropin releasing hormone receptor, *FSHR* follicle stimulating hormone receptor, *LHR* luteinizing hormone receptor, *AR* androgen receptor, *ERα* oestrogen receptor α, *ERβ* oestrogen receptor β, *PR* progesterone receptor, *MR* mineralocorticoid receptor, *TR* thyroid hormone receptor, *GR* glucocorticoid receptor

CYP11A1) has been reported in endometrial cancer tissue compared to the adjacent precancerous tissue [32]. Further studies are required to confirm these findings and to elucidate the role progesterone metabolising enzymes play in altering the intra-tumour bioavailability of exogenous progesterone in endometrial cancer.

6.3.2 Oestrogen Intracrinology

The final intra-tumour oestrogen concentration and activity in endometrial cancer cells are altered due to changes in several hormone metabolic pathways (See Fig. 6.2). These include:

1. The inter-conversion of E2 and E1, regulated by a group of 17βHSD isoforms with different catalytic efficiency [34];

2. Local oestrogen synthesis via two main pathways:

(a) Aromatase pathway—where androgen prohormones DHEA, androstenedione and testosterone are converted to oestrogens by aromatase and aided by 17βHSDs (See Fig. 6.2) and
(b) Sulphatase pathway—which activates sulphated precursors estrone sulphate (E1S) and DHEAS to E1 and DHEA, respectively, and then can subsequently be converted to E2 [35];

3. Local inactivation of oestrogens and DNA damage can be initiated by failure of the catechol-oestrogen deactivation in endometrial cancer by catechol-O-methyltransferase (COMT) and glutathione transferase (GT), resulting in the formation of quinone compounds under the effect of peroxidases or via non-enzymatic pathways [36].

6.3.3 Androgen Intracrinology

In addition to the contribution to the local oestrogen synthesis, androgen prohormones serve as important precursors for testosterone and the most potent naturally occurring AR ligand, DHT (See Fig. 6.2). Before terminal inactivation by conjugation with glucuronide and sulphate compounds, metabolites of DHT retain affinity to steroid receptors and can activate ER as a substitute in hormone depravation conditions [37].

6.4 Hormone Receptors

Steroid and non-steroidal hormones exert most of their effect via their respective cognate receptors (See Fig. 6.3). The signalling pathways, structure, isoforms, expression and prognostic value of these receptors in endometrial cancer are discussed in this section.

6.4.1 Steroid Receptors

Steroid hormone receptors (ER, PR, AR and GR) are members of the nuclear hormone receptor superfamily and share the common, evolutionarily conserved structural and functionally distinct domains as the other members of the superfamily (See Fig. 6.3). This includes a central, highly conserved DNA binding domain (DBD) which binds to the same ligand responsive element in the target gene promoters; multifunctional ligand-binding domain (LBD); the ligand-dependent AF-2 at the C-terminal; constitutively active AF-1 at the N-terminal; and flexible-hinge D-domain in between LDB and DBD.

6.4.1.1 Oestrogen Receptors

Cellular signalling of oestrogen is mediated through two receptors: ERα (ESR1) and ERβ (ESR2) [38, 39]. Despite the close homology between the two isoforms, ESR1 gene is located on chromosome 6 whereas ESR2 gene is located on chromosome 14.

The classical pro-proliferative action of oestrogen on the endometrium is exerted via ERα but it also induces ERβ expression. Ligand activated ERβ counteracts ERα action on the same promoter by altering co-activator [40] and key transcription factor recruitments [41]. Hence, the guardian effect of ERβ on the endometrial cellular homeostasis has been of particular interest [42].

The expression of ERα and ERβ is evident in low-grade endometrioid endometrial cancers [43–46], whereas high-grade endometrioid and non-endometrioid cancers have a significantly lower yet persistent expression of both isoforms [45]. The change in the relative expression of these isoforms represented by ERα/ERβ has a prognostic value. ERα/ERβ ratio is reported to be lower in high-grade cancers and associates with a poor patient outcome [47–51].

Alternative splicing of ESR1 and ESR2 pre-mRNA allows these genes to encode diverse proteins which may subsequently regulate the wild-type proteins [52]. The exon skipping variety constitutes the majority of ERα splice variants, out of which ERαΔ5, ERαΔ4, ERα36 and ERαΔ7 are the most studied in the endometrium. Overall, more ERα splice variants are found in malignant tissues compared with normal or premalignant endometrial tissues [53, 54]. ERβ variants (ERβ1, ERβ2, and ERβ5) display similar expression patterns to ERα in endometrioid endometrial cancer (EC) samples. ERβ1 and ERβ2 immunoexpression was higher in low-grade EC, whereas ERβ5 expression was constitutively intense regardless of the grade [55]. Disruption of the subtle equilibrium of these splice variants could be a contributing factor in EC development.

Interestingly, ER expression has been reported as the best predictor of response to sequential endocrine therapy (medroxy progesterone acetate (MPA)/tamoxifen) for patients with advanced or recurrent Endometrial cancer, whereas PR showed limited value [56]. This is likely to be due to the requirement of an active ER to maintain PR expression, which allows MPA action.

6.4.1.2 Progesterone Receptors

PR was first purified and cloned in 1975 [57]. Two protein isoforms have been identified, PR-A and PR-B, produced from a single gene by transcription at two

distinct promoters [58–60]. In the endometrium, the ratios of the individual isoforms vary according to the reproductive, hormonal status [61, 62] and during carcinogenesis [63].

PR-B acts as an activator of progesterone-responsive genes, whereas PR-A has a strong repressor effect on PR-B and ER transcriptional activity [64]. The precise mechanism underlying the differential activities of the two PR isoforms is not fully understood. Studies have suggested that the conformational changes of PR-A and PR-B inside the cells alter recruitment of co-activators and co-repressors and therefore transactivation functions [65].

Generally, PR expression is downregulated in less-differentiated endometrial cancers [45]; nonetheless, the debate about the expression of PR isoforms in advanced EC is continuing with studies reporting: (1) the loss of both isoforms in endometrial cancers [56, 66], (2) alteration of the relative expression of the isoforms [67] and (3) a slightly higher PR-B level in advanced endometrial tumours [68].

The prognostic value of PR has long been recognised [69]. Although there is compelling evidence suggesting a significant, independent, prognostic role for PR [70, 71], the predictive value for PR to guide successful endocrine therapy has not yet been fully determined. In this respect, the essential, standard quantification methods and best cut-off points in assessing PR expression in endometrial tumours have not yet been formalised. Such assessment could be of value when progesterone is first-line treatment, for example, in fertility sparing treatment. The recent ESGO-ESMO recommendation, however, limits PR assessment to advanced or recurrent disease [72]. The argument against the assessment of PR in fertility sparing cases is that 2/4 (50%) patients who showed a response to progesterone were PR negative; however, 5/5 (100%) of patients who responded were PR positive and the difference between the two groups was significant ($P = 0.008$) [73]. The small sample size ($n = 9$) included in the referenced trial and the absence of confirmatory studies makes it difficult to form a firm conclusion.

6.4.1.3 Androgen Receptors

AR gained interest in the field of gynaecology with the introduction of danazol as a treatment for endometriosis in the early 1980s [74]. The AR gene is located on the X chromosome at the locus Xq11-Xq12 which encodes a 110-kDa protein consisting of 919 amino acids [75]. The first description of AR expression in the human endometrium was documented by Horie et al. in 1992 [76]. Successive reports characterised AR in the stroma of premenopausal endometrium across the cycle [77–79] and reported its emergence in the postmenopausal glandular epithelium [45]. AR is expressed by low-grade endometrioid endometrial cancers [45, 80, 81] whereas its loss is a feature of high-grade EC, particularly the non-endometrioid subtypes [45]. The association of AR loss with poor EC patient outcomes proposes this protein as a prognostic indicator [45, 82]. Multiple splice variances of AR have been described in prostate cell lines [83], but evidence for their expression in normal and malignant endometrial tissue is lacking.

6.4.1.4 Corticosteroid Receptors (Glucocorticoid and Mineralocorticoid Receptors)

Cortisol activates glucocorticoid receptor (GR) and aldosterone primarily activates mineralocorticoid receptor (MR), although it does have some responsiveness to cortisol [84]. The GR is encoded by the NR3C1 gene located on chromosome 5 (5q31) and both of the GR isoforms, GR-α and GR-β, have been identified in the stromal compartment of the endometrium [85–87]. The active receptor GR-α, controls glucocorticoid-induced cellular apoptosis [88], and may function as a tumour suppressor by ensuring accurate chromosome segregation during mitosis [89]. GR-β isoform, which functions as the main negative inhibitor of GR-α, controls the glucose metabolism through increasing insulin sensitivity, and decreases hepatic gluconeogenesis [90]. The expression of GR is regulated by cortisol catalyzing enzymes, 11β-hydroxy dehydrogenase type 1 (11βHSD1) and type 2 (11βHSD2) [91] via regulating the local cortisol levels. The highest expression of GR and 11βHSD1 are observed in the menstrual phase, allowing cortisol to bind to GR, and thus is postulated to mediate an anti-inflammatory action [87].

6.4.2 Thyroid Hormone Receptor (TR)

Human nuclear TRs, implicated in the genomic pathway, are encoded by TRα and TRβ genes located on human chromosomes 17 and 3, respectively. These receptors function as ligand-dependent transcription factors that form heterodimers with the retinoid X receptor (RXR) or complexes with nuclear co-activator proteins such as p300 and steroid receptor co-activator-1 (SRC-1) and binds to thyroid hormone response elements (TRE) located in the target gene promoters [92].

Non-genomic transcription independent effects are mediated through cell surface αvβ3 receptor, which has a significantly higher affinity for T4. It activates a transporter system within the plasma membrane, resulting in either extracellular actions (involving vascular growth factor receptors and integrins) or intracellular events (cytoplasmic/nuclear trafficking of specific proteins, or activation of signal transducing kinases (MAPK, ERK1/2, Aktd)) [93]. Thyroid receptors therefore can influence a wide range of important regulatory proteins, from basic fibroblast growth factor (βFGF; FGF2), matrix metalloproteinase-9 (MMP-9), to oncogenes or proto-oncogenes. TSH receptor and thyroid hormone receptor are expressed in the human endometrium and their concentration is affected by the menstrual cycle with the highest levels seen during the mid-secretory phase [19].

6.4.3 Insulin Receptors

The insulin receptor is a member of the ligand-activated receptor and tyrosine kinase family of transmembrane signalling proteins. It is located in the plasma membrane and is composed of two pairs of subunits [94, 95]. Insulin receptors are

located in primary target cells such as adipocytes, hepatocytes and skeletal muscle cells as well as in non-typical tissues such as the endometrium [94]. The main physiological role of the insulin receptor is metabolic regulation. The ligand activation phosphorylates the insulin receptor resulting in engagement of the effector molecules [95]. High concentrations of insulin downregulate its own receptor in adult cells, and muscular exercise, diet, thyroid hormones, glucocorticoids, androgens, oestrogens and cyclic nucleotides are all able to regulate insulin binding [94]. Interestingly, the insulin-induced downregulation of receptors is reversed in immature foetal cells where a paradoxical upregulation is demonstrated with high insulin. Insulin binding sites are also expressed in the endometrial stroma of women with Endometrial cancer [52]. The association of elevated IR-A levels with cell proliferation and tumourigenicity may be causally linked to its effect on the proportion of cells in S phase and the activation of the Akt pathway [96].

6.4.4 GnRH Receptors

The GnRH receptor (GnRHR) is a member of the G-protein coupled receptor (GPCR) family and functions in the inositol phosphate signalling pathway [97]. GnRHR isoforms, GnRHR I and GnRHR II, are desensitised through GnRH-induced phosphorylation [98]. The GnRHRs are present in the extra-pituitary reproductive tissues like the endometrium [12], placenta, ovary and breast [99–103]. Both GnRHRs have been identified in the endometrium throughout the cycle, and in gynaecological tumours [103–106]. Studies examining physiologic signalling of GnRHR in extrapituitary tissues only used GnRH agonists and/or antagonists with long half-lives, often at pharmacologic levels, and are thus flawed.

6.4.5 FSH/LH Receptors

FSH and LH act through specific 678 and 675 amino acid residues, the long receptors belonging to the leucine-rich-repeat-containing GPCRs (LGR) subfamily [107]. The FSH–FSHR complex forms dimers which may participate in transmembrane signal transduction and thus is more specific, whereas both LH and human chorionic gonadotropin (hCG) act through the single LHR. Activation of both receptors may influence Gs/adenylyl cyclase/cAMP/PKA pathways and their expression in non-gonadal tissues such as the endometrium has been reported [108].

6.4.6 Melatonin Receptors

Melatonin exerts its effects through two high affinity G protein coupled receptors, MT1 and MT2. The MT1 receptor is encoded by MTNR1A gene, located on chromosome 4 (4q35). MT2 receptor is encoded by the MTNR1B gene, located on chromosome 11 (11q21-q22) [109–111].

Rat endometrial stromal cells express MT1 receptors [112], which are responsible for the anti-proliferative effects of melatonin on the growth of these cells in vitro [113]. The ERα positive EC cell line, Ishikawa, expresses the MT1 receptor, but does not express the MT2 receptor. Melatonin upregulates the MT1 receptor, and downregulates ERα receptor, which suggests an anti-proliferative effect of melatonin on the endometrium, possibly via the MT1 receptor [114].

6.4.7 Steroid Receptor Signalling

The molecular action of steroid hormones is mediated through their intracellular receptors [39]. In the absence of the ligand, each receptor monomer is associated with a protein complex that contains a chaperone. This receptor complex is incapable of binding to DNA and is either located in the cytoplasm (AR and GR), loosely bound in the nucleus (ER and PR) or cytoplasmic/membrane bound (ER and PR) [40]. The steroid hormone signalling cascade starts when the hormone diffuses passively across the plasma membrane and binds to the cognate receptor. The hormone–receptor complex induces conformational changes and leads to receptor activation and subsequent molecular changes. Several signalling pathways have been postulated which can be broadly classified into [39];

1. *Genomic pathway*: is the standard and the best characterised pathway via which steroid receptors act as ligand-inducible transcription factors. Inside the nucleus, activated steroid receptors bind as homodimers to the respective hormone responsive element located in the relevant gene promoters and initiate recruitment of co-activators, co-repressors and chromatin-remodelling factors and directly regulate gene transcription (classical pathway). Steroid receptors can also initiate gene transcription indirectly by interacting with other transcriptional factors such as specificity protein 1 (SP-1) and this is termed as the non-classical pathway
2. *Non-genomic pathway*: is a less well characterised pathway that mediates a more rapid and reversible response without the need for nuclear translocation. Activated steroid receptor in the cytoplasm or plasma membrane can stimulate second messenger cascades which subsequently interact with several signalling pathways such as phosphatidyl-inositol 3-kinase (PI3K)/Akt.

In addition to these main ligand-induced signalling pathways, sex steroid hormone receptors can initiate signal transduction in the absence of their ligands (hormone-independent pathway). The activation of this pathway is influenced by several factors such as the type of the cell, promoter and activator [115].

6.4.8 The Normal Endometrial Response to Steroid Hormones

6.4.8.1 Premenopausal

Premenopausal endometrium is characterised by the presence of two functionally diverse layers, the superficial functionalis and the deeper basalis [116]. The

functionalis is proposed to be exceptionally sensitive to hormones, exemplified by the regular monthly cyclical changes of proliferation, differentiation, followed by menstrual shedding and regeneration when pregnancy is not established, all of which are meticulously regulated by the ovarian hormones [117]. The basalis on the other hand, is thought to be less responsive to these hormones. It exists throughout a woman's life and is postulated to be the germinal layer of the endometrium from which a new functionalis is generated from [117, 118]. Further studies are required to explain the different responsiveness to the hormones by these two endometrial layers in which hormone intracrinology is expected to play a role.

6.4.8.2 Postmenopausal (PM)

The PM hormonal milieu supporting the thin PM endometrium (the remaining basalis) is characterised by the presence of low oestrogen, adrenal androgens and the absence of progesterone [1, 42]. Compared with many other reproductive tissues, the endometrium does not undergo senescence and a fully operational functionalis can be restored with the administration of the appropriate exogenous hormones even decades after the menopause [119]. This apparent preservation of both the hormone responsiveness and the regenerative potential, however, is likely to be the basis for the high incidence of carcinogenesis observed in the PM endometrium.

The hypothesis of hormone-induced carcinogenesis was first documented by Bittner [120] in 1948 and refined by Henderson et al. [121] in 1982. The hypothesis states that "neoplasia is the consequence of excessive hormonal stimulation of a particular target organ, the normal growth and function of which are under hormonal control. The response of this end organ (e.g., endometrium, breast) to the proliferative effects of the hormone is a progression from normal growth to hyperplasia to neoplasia" [122]. Over the past three decades, researchers have been trying to understand the mechanisms, circumstances and consequences of hormone-induced neoplasia, and several hormonal factors were found to contribute to the malignant transformation of endometrial cells.

6.4.9 Oncogenic Roles of Oestrogen

The basic impact of oestrogens on proliferation and growth of reproductive tissues was recognised in the 1950s [123], predating the identification of oestrogen receptors [124].

The most plausible theory of oestrogen-induced carcinogenesis remains to be the mitotic action of oestrogen via the classical [125] or non-classical [126–130] nuclear ERα pathways, unopposed by progesterone. Progesterone counteracts this trophic drive of E2, therefore a relative increase in E2 over progesterone levels (due to endogenous or exogenous factors) is associated with an excessive and prolonged proliferation of endometrial cells.

Non-genomic oestrogen signalling is another oestrogen pro-oncogenic pathway. The non-transcriptional response to oestrogen via membrane located ER activates

the extracellular signal-related kinase (Erk) 1/2 signalling pathway which plays a critical role in cell proliferation by regulating cell growth and cell cycle progression [131]. G protein-coupled receptor 30 (GPR30), an orphan membrane receptor, has also been implicated in this pathway [132]. GPR30–oestrogen complex was shown to stimulate EC cell proliferation and promote invasion by increasing the production and activity of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) via the MEK/ERK MAPK pathway [133].

Emerging evidence has advocated the involvement of DNA methylation status in oestrogen signalling as a possible pathway in endometrial carcinogenesis. Defective chromatin architecture at the ER target locus may have a key role in endometrial proliferative disease [134]. Age independent hypermethylation of ESR1 promoter has been reported in 90% of Endometrial cancer in contrast to observations in breast cancer [135–137] (See Fig. 6.4). This further highlights the differences in hormone regulatory mechanisms between various hormonally active tissues, which to some extent preclude the possibility of generalising the findings in one tissue to others. Oestrogen-associated genotoxicity is another emerging theory in oestrogen-induced carcinogenesis. Endometrial tumour initiation has been proposed to be a consequence of metabolic activation of catechol-oestrogens, semiquinolones and quinolones [138]. Several studies have shown that 4-hydroxylated oestrogen, catalysed by cytochrome P450 1B1, is able to induce DNA damage [139–142]. Importantly, this is not a product of the main hepatic and extrahepatic metabolic pathway of E2, but occurs in organs prone to oestrogen-associated cancer such as the endometrium [143, 144]. An increase in carcinogenic catechol oestrogens is associated with DNA damage at a specific DNA region (codon 130/131) on the tumour suppressor gene PTEN, which is frequently found to be mutated in EC [145–147].

6.4.10 The Tumour Suppressive Role of Progesterone

The clinical implementation of progesterone as an inhibitor of endometrial carcinogenesis has emerged from the strong association between conditions associated with higher progesterone exposure, such as ovulation and high parity and lower EC risk [148]. The lack of endogenous progesterone synthesis, consequent to anovulation with unperturbed oestrogen production, can lead to excessive and prolonged proliferation of the endometrial cells which may progress to hyperplasia [149].

Direct antiproliferative action of progesterone on the endometrial epithelial cells is exerted via the classical genomic action of PR (See Fig. 6.4). PR isoforms sensitise EC cells to apoptosis; induce cell cycle arrest [150]; regulate p53 via non-classical genomic action [151]; regulate several transcriptional factors and adhesion molecules involved in tumour progression and metastasis (AP-1, NFκB, integrins and cadherins); and PR-B promotes cell differentiation by inducing Wnt inhibitory proteins such as FOXO1 [152].

The crosstalk between epithelial and stromal cells is essential for the normal endometrial function of progesterone. Evidence from tissue recombination studies

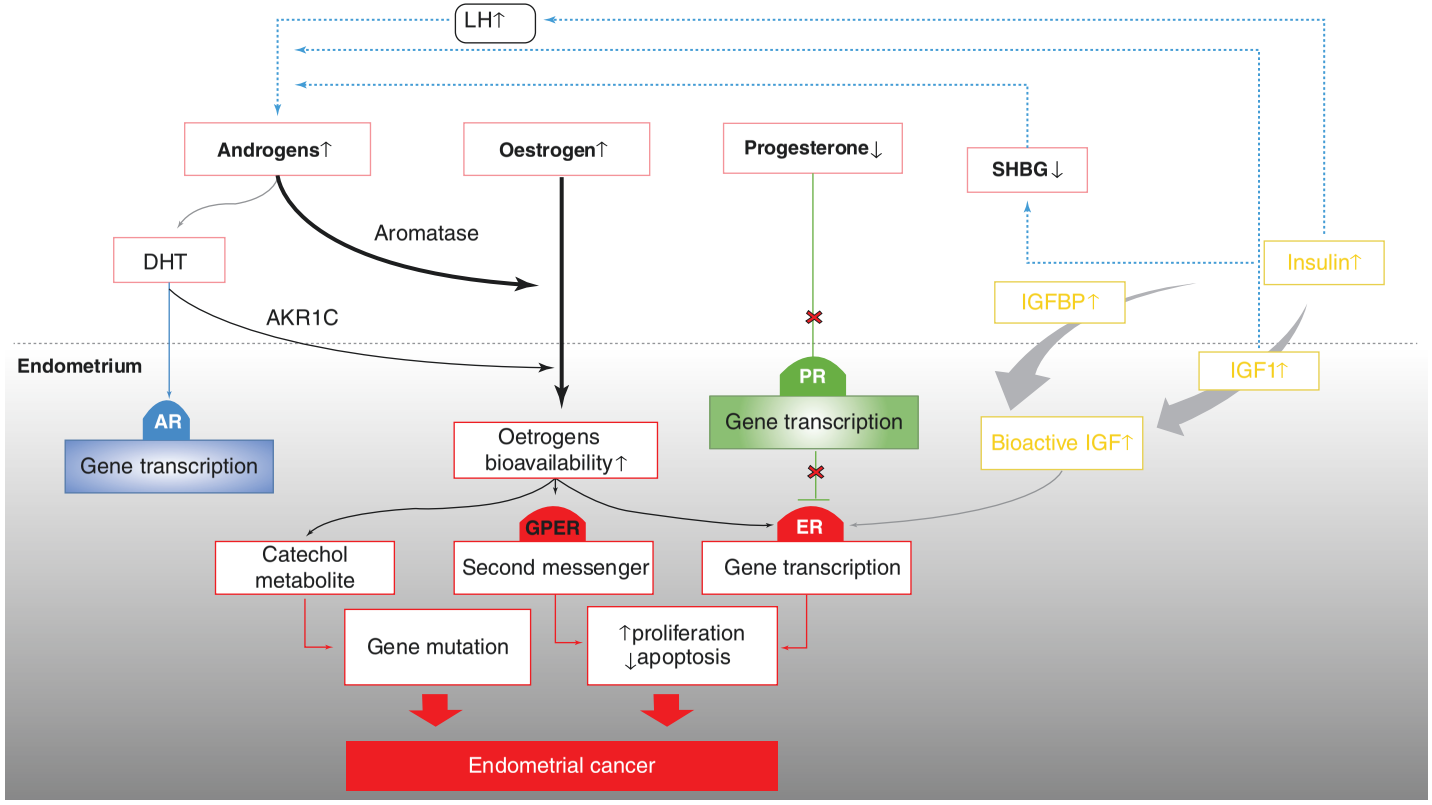

Fig. 6.4 Different hormonal and metabolic pathways associated with disturbed steroid hormones homeostasis in favour of oestrogen pro-oncogenic pathway [1]. *AKR1C* aldoketoreductase1C, *DHT* dihydrotestosterone, *GPER* G protein coupled oestrogen receptor, *IGF-1* insulin-like growth factor 1, *IGFBP* insulin-like growth factor binding protein, *LH* luteinizing hormone, *SHBP* steroid hormone binding protein

utilising PR knockout (PRKO) mice with selective inactivation of endometrial epithelial and stromal PR suggests that stromal PR is a prerequisite for the anti-oestrogenic effect of progesterone and regulates epithelial cell apoptosis [153–155]. Progesterone suppresses the production of stromal growth factors that act as paracrine mediators of the mitogenic effects of oestrogen on the epithelium by inducing the basic helix-loop-helix transcription factor, Hand2, expression in the endometrial stromal cells [156].

Epigenetic modification of PR is one of the suggested mechanisms of impaired progesterone protective function in EC either by methylation of PR-B promoter or post transcriptional deactivation of PR isoforms via miRNA or small ubiquitin-like modifier proteins [137, 157]. In conclusion, progesterone's insufficiency as well as aberrant cognate receptor expression and activity have a pivotal role in EC development.

6.4.11 Hyperinsulinism

Hyperinsulinism, associated with either diabetes mellitus or polycystic ovarian syndrome (PCOS), plays an important role in endometrial carcinogenesis as it potentiates mitotic activity in the glands and stroma by increasing the activity of insulin-like growth factor 1 (IGF-1) [158–160] (See Fig. 6.4). Excess insulin stimulates the androgenic activity of the theca cells; elevates serum-free testosterone levels through decreased hepatic sex hormone-binding globulin (SHBG) production; amplifies LH and IGF-I-stimulated androgen production; and enhances serum IGF-I bioactivity through suppressed IGF binding protein production [159, 161, 162]. The two isoforms of IR-A and IR-B are co-expressed in EC, but the overexpression of IR-A promote the proliferation of Endometrial cancer cells by insulin [96, 163, 164]. Therefore, an excess in insulin signalling can result in endometrial changes with a pro-proliferative, pro-survival phenotype and inflammatory changes akin to unopposed oestrogen.

6.4.12 Hyperandrogenism

The association between high circulating androgen levels and EC is well established [165–169], however the *in vivo* and *in vitro* evidence to support the carcinogenesis effect of androgens in the endometrium is weak [170]. Administration of exogenous testosterone and androstenedione either to PM [171] or transgender women [172] has not increased the EC risk. By contrast, emerging evidence suggests AR to be a favourable prognostic indicator [45, 82]. Along these lines, the expression of 5α reductase enzyme, which is responsible for the conversion of testosterone to the most potent endogenous androgen DHT, is associated with better patient outcomes in EC [82]. *In vitro* studies show different androgens to have antiproliferative effects on primary premenopausal endometrial cells [173] and EC cell lines [174].

Therefore the most plausible explanation for the positive association between serum androgens and EC is the increased bioavailability of unopposed oestrogens via peripheral conversion of androstenedione and testosterone, to E1 and E2 (See Fig. 6.2). Studies have shown higher levels of aromatase [175, 176] and aldo-ketoreductase (AKR1C) [177] enzymes expression in neoplastic endometrial cells compared with normal endometrium. This may increase the local production of oestrogenic compounds with relatively higher affinity to ER instead of AR and therefore augment an oestrogenic pathway [178]. This pathway is not limited to type I EC, since high expression of aromatase is also observed in type II, which may allow this subtype of EC to increase local oestrogen biosynthesis and hence proliferation [179].

6.4.13 The Role of Other Hormones in Endometrial Carcinogenesis

6.4.13.1 GnRH

GnRH may regulate the endometrium via autocrine or paracrine routes. Endogenous GnRH may have a negative role in the autocrine system interfering with the growth factors. GnRH-2 has a direct effect on EC cells by inducing apoptosis, arresting the cell cycle and inhibiting the cellular proliferation [101, 180]. Activation of ERK1/2 and p38 MAPK via integrin beta 3 and focal adhesion kinase (FAK) is one of the suggested pathways [181]. Therefore, GnRH ligands may be useful for treating EC. Controversially, a recent study has shown that GnRH-2 increases EC cells proliferation by stimulating epidermal growth factor release [182] and others concluded that GnRH-2 promotes cell migration and invasion by inducing different metastasis related proteinase and vascular endothelial growth factor (VEGF) resulting in neo-angiogenesis [183]. Endometrial epithelial GnRH mRNA levels appear to be upregulated by progesterone, and about 80% of endometrial cancers express both GnRH and GnRHR as a part of the autocrine system [184]. Therefore, further studies clarifying the controversies associated with the role of this hormone and its therapeutic potential in EC are needed.

6.4.13.2 Luteinizing Hormone/Human Chorionic Gonadotrophin

The literature on gonadotrophin levels associated with EC is contradictory, some report lower FSH levels suggesting an altered hypothalamic function [185] whilst others report high gonadotropin levels in endometrial hyperplasia and carcinoma [186].

LH/hCG receptors (LH-R) are expressed in 80% of endometrial cancers [187, 188] in a grade specific manner and may regulate the invasiveness of EC cells [189]. The *in vitro* work examining the direct effect of LH-R and LH has shown that the over-expression of the LH-R increases the ability of EC cells to undergo local invasion and metastatic spread in animal models. Likewise, LH withdrawal strongly inhibits local and distant metastatic spread of tumours [190]. LH upregulates its

own receptor, therefore it is an important target in relation to the PM period where the levels of LH remain elevated (See Fig. 6.4).

6.4.13.3 Thyroid Stimulating Hormone (TSH) and Thyroid Hormones (TH)

Elevated TSH levels in patients with EC have been independently associated with poor disease-specific survival [191]. TSH may influence endometrial carcinogenesis and invasiveness via its action on adipose tissue and the subsequent release of leptin [192]. However, TSH and TH receptors have been identified in endometrial tissues, supporting a more direct effect on cell proliferation. T4 can bind to integrin αvβ3 and cause MAP kinase-dependent phosphorylation of the nuclear oestrogen receptor [193]. Simultaneously, the complex T3/TR initiates the genomic pathway and regulates lipocalin 2, a tumour-associated protein, that enhances tumour cell migration and invasion [194]. These remarks warrant further studies examining a direct role for TSH and thyroid hormone on endometrial carcinogenesis [195–197].

6.4.13.4 Melatonin

The anti-tumour effect of melatonin has been demonstrated in many cancers, through interacting with membrane and nuclear receptors [198]. In breast cancer, this is related to the oestrogen receptor status and therefore may be relevant to most endometrial cancers, which are also oestrogen-dependent. In the ERα positive EC cell line Ishikawa, treatment with melatonin significantly inhibits cell growth and the effect is reversed by administration of 17-b estradiol [199], inferring that melatonin acts via the oestrogen receptor to decrease EC proliferation.

Melatonin levels have been shown to decrease in the postmenopausal period [200] when EC commonly occurs. Women with EC have lower melatonin levels. Night shift workers who have a lower level of melatonin also appear to have an increased risk of developing EC [201]. Melatonin administration in addition to harmone replacement therapy (HRT) was associated with reduced body mass, intraperitoneal fat, reduced endometrial proliferation and prevented the appearance of histological atypia of the endometrium in an ovariectomised rat model. This indicates that melatonin may have a prophylactic role in preventing EC in postmenopausal women [202].

6.4.13.5 Corticosteroids

Glucocorticoids have anti-inflammatory, immunosuppressive effects, and cause cellular apoptosis [203]. Glucocorticoid receptors have inhibitory effects on the growth of lymphoid cancer cells, and other solid tumours [204]. These anti-proliferative effects may also be applicable to EC. In the GR-positive EC cell line, Ishikawa, treatment with dexamethasone causes downregulation of the cellular adhesion molecule N-cadherin, and upregulation of the anti-proliferative factor, upstream c-fos relating transcription factor (USF-2), suggesting glucocorticoids to have a similar growth inhibitory action as progesterone in EC [205]. Further examination of GR

and glucocorticoid treatment in EC will help to examine their therapeutic implication further.

6.5 Hormonal Aberrations Relevant to EC Risk Factors

6.5.1 Endogenous Hormones

Many of the well-known high-risk endogenous conditions (See Table 6.1) for developing EC are associated with one or more of the specific hormonal aberrations mentioned above [209]. Early age at menarche, late age of menopause, nulliparity, anovulation, history of infertility and presence of oestrogen-producing tumours increase the risk of EC, presumably due to the prolonged or unopposed exposure to oestrogen [209, 210]. Conversely, pregnancy, including termination of pregnancy, decreases the risk by prolonged exposure to progesterone [211].

Polycystic ovarian syndrome (PCOS) has been defined as the strongest independent endogenous risk factor for the development of EC [208]. Anovulation, hyperandrogenism and hyperinsulinemia that commonly associate with PCOS, create a vicious cycle of hormonal abnormalities that can induce endometrial carcinogenesis [212]. Diabetes and obesity, both independent risk factors for EC, are associated with hyperinsulineamia [207] and alter hormonal homeostasis at several levels. Peripheral aromatisation of oestrogen remains the main carcinogenic pathway in obesity; however, the involvement of cytokines and adipokines is increasingly being reported [206]. The premalignant precursor of endometrioid EC, endometrial

Table 6.1 The known high-risk conditions for developing EC and their associated hormonal aberrations

Factor	Risk	Hormone-associated mechanism
Obesity	RR: 1.59 for every 5 kg/m^2 increase [206]	↑ Peripheral oestrogens production ↑ Insulin and growth factors ↑ Inflammatory cytokines ↑ Leptin/adiponectin ratio
Diabetes	RR: 1.89 [207]	Obesity → oestrogen/progesterone imbalance Hyperinsulinism and IGF-1
PCOS	OR: 2.79 OR: 4.05 for young women <54 years old [208]	Unopposed oestrogens Obesity → ↑ oestrogen Hyperinsulinism, Hyperandrogenism
Hyperplasia	Without cytological atypia RR: 1.01–1.03 With cytological atypia RR: 14–45 [187]	Unopposed oestrogens Obesity → ↑oestrogen ↑ Insulin ↑ LH/FSH ratio ↑ Endometrial aromatase activity ↓ Melatonin

hyperplasia, with cytological atypia is almost invariably associated with unopposed oestrogen and co-exists with EC in up to 50% of cases [213, 214].

6.5.2 Exogenous Hormones

The main pharmacological agent that has been associated with an increased risk of endometrial carcinogenesis is unopposed exogenous oestrogens or agents that mimic oestrogens. Potent oestrogens are never indicated in isolation without sequential or concomitant progesterone in hormone replacement for women having an intact uterus. Yet there are several non-steroidal non-hormonal compounds, termed selective oestrogen receptor modulators (SERMs), licenced for osteoporosis or as adjuvant treatment/chemoprevention of breast cancer. They bind to ER causing either an agonistic or antagonistic effect depending on the availability of oestrogen [215]. Although the earlier SERMs, such as tamoxifen, cause endometrial proliferation with pathological changes ranging from hyperplasia and polyps to invasive carcinomas and sarcomas in the endometrium due to its ER agonist activity in the uterus [216], the newer SERMS (Raloxifene, Bazedoxifene and Ospemifene) are reported to have neutral effects on the endometrium [217, 218]. Furthermore, the trophic effect of tamoxifen is only seen in postmenopausal women and no robust evidence for increasing EC in premenopausal women exists. Therefore tamoxifen treatment in these women requires no additional monitoring beyond routine gynaecological care [219].

Tibolone, a synthetic steroid with oestrogenic, some progestogenic and androgenic properties, is commonly used to prevent climacteric symptoms and osteoporosis, but has also been reported to increase the risk of EC [220]. However, a previous Cochrane Systematic Review failed to depict any clear evidence of association given the low number of events [221].

Selective progesterone receptor modulators (SPRM), such as mifepristone, have partial agonist/antagonist activity and the observed endometrial effect depends on the availability of progesterone [77]. Long-term use of high-dose mifepristone thickens the endometrium, although the associated histology shows cystic glandular atrophy with a reduction in glandular mitosis. Nevertheless, concerns have been raised regarding a potential trophic effect of SPRMs on the endometrium [222]. Second generation SPRM, ulipristal acetate, licenced for preoperative or intermittent treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age does not increase the occurrence of endometrial features of concerns [223]. There are reports of hyperplasia without atypia and polyps with prolonged treatment, yet the endometrium reverted back to normal 6 months after treatment (PEARL III). Therefore, until further conclusive data is available, clinicians using high-dose prolonged therapy with SPRMs in women need to be aware of possible endometrial changes similar to the ones following tamoxifen treatment [224, 225].

6.6 Conclusion

EC is a common hormonally responsive gynaecological malignancy. Being a target organ for ovarian steroid hormones and a plethora of other hormones, the normal and pathological human endometrial function is likely to be relevant to the levels and action of these hormones. The development of novel preventative and diagnostic strategies as well as stratifying women for post-surgical treatment requires our full and detailed understanding of intertwined action of these hormones on the endometrial cell subtypes. Thus accelerated efforts by EC researchers to answer many unclear areas highlighted in this chapter are needed to improve the outcome of millions of women suffering from this devastating condition.

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