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Review

Progestogen deficiency and endometrial cancer risk

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ABSTRACT

There is a close relationship between the amount of estogen and progesterone secreted by the ovary from puberty to menopause and the development of hyperplastic endometrium of all types and finally endometrial cancer. The endogenous endocrine pattern reflects progesterone deficiency (corpus luteum deficiency). Such deficiency can also develop when treatment with exogenous estrogen and progestogen is done and a deficiency of the progestogen in comparison to the used estrogen is induced in pre- and postmenopausal women. This risk is particular accentuated in the climacteric female when the endocrine milieu was unfavorable in the years before (menstrual cycle disorders, PCOS, obesity, no full-term pregnancy, no breast feeding, etc.).

However, there are the additional factors, which modify the biological end result: "Progestogen deficiency". One main factor is the level of SHBG determined by the amount of free, biologically active estradiol. A low level of SHBG is for instance induced by high body weight. Therefore, the amount of overweight correlates with increased risk of endometrial hyperplasia and finally endometrial cancer. In addition, increasing body weight negatively affects proper ovarian function leading to corpus luteum deficiency and this in addition increases the risk of endometrial cancer. The classical risk increase for endometrial cancer is associated with oligomenorrhea or polymenorrhea combined with corpus luteum deficiency or anovulation. Therefore, women with PCOS are at increased risk for endometrial cancer in the pre- and postmenopausal years. Examples from the therapeutic point of view have been the risk increase found with biphasic estrogen high-dosed oral contraceptives with a long estrogen phase and a short progestogen phase. In climacteric females estrogen-only treatment results in a predictable increase in endometrial cancer risk. Therefore, it is mandatory to use estrogen/progestogen combinations. The lowest risk is achieved when a continuous estrogen/progestogen regimen is used. In addition, the lowest dose of estrogens for the individual woman should be chosen.

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1. Introduction

Endometrial tissue growth and proliferation as well as differentiation is primarily dependent upon estrogen and progesterone effects naturally regulated by the quality of menstrual cycle function and other factors such as obesity, which is associated with a decrease of SHBG and therefore a relative increase of free biologically active estradiol, but also by extraglandular steroid metabolism converting androgens to estrogens. Also variations in estradiol metabolism might play a role. In addition, there can be exogeneous estrogens and xenoestrogens as summarised in Table 1.

Regulation and differentiation of the estrogen-stimulated endometrium is dominated by progesterone or progestins. In the human there is direct secretion by the ovaries and to a certain extend by the adrenal and in pregnancy by the placenta in large quantities. A further source is the xenoestrogens. Endometrial cancer is mainly a disease in the postmenopausal years with a peak incidence around 60 years of age. 5% of the women with endometrial cancer are younger than 40 years and 15% are younger than 50 years.

Endometrial hyperplasia, particular the complex endometrial hyperplasia with atypia, is the precursor of endometrial cancer. All the endometrial changes are based upon the biologically induced

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Table 1
Sources of estrogens.

1. Direct glandular (ovary) production and secretion.
2. Extraglandular steroid metabolism. Conversion of androgen to estrogen outside the ovaries in various tissues of the body depending on the enzyme aromatase
3. Activation of estrogen in the tissues by the conversion of estrone to estradiol.
4. Inactivation of estrogen by the conversion of estradiol to estrone.
5. Exogenous estrogens.
6. Xenoestrogens.

Table 2
Risk factors of endometrial hyperplasia and endometrial cancer.

A. Exogenes factors
1. Early menarche (early estrogen stimulation).
2. Late menopause (late estrogen stimulation).
3. Obesity (increased extraglandular estrogen production and lower SHBG resulting in increased levels of biologically free estradiol).
4. Anovulation (chronic estrogen stimulation and lack of progesterone)
5. Nulliparity (lack of 9 month dominant progestogen effect by pregnancy).
6. Estrogen-producing tumor (chronic estrogen overstimulation and lack of progesterone).
7. Insulin resistance/diabetes mellitus (chronic estrogen stimulation and lack of progesterone).
8. Hyperandrogenemia (increased conversion of androgens to estrogens, decreased SHBG, menstrual cycle dysfunction and by this lack of progesterone.
B. Exogeneous factors
1. Estrogen treatment (chronic estrogen stimulation and lack of progesterone).
2. Tamoxifen (chronic estrogen stimulation and lack of progesterone).

Table 3
Effect of medroxyprogesterone acetate (MPA) and cyproterone acetate (cyproterone acetate) on the histology of endometrial hyperplasia after 60 days (according to [15]).

Histology	MPA (10 mg/day)	CPA (25 mg/day)
Endometrial hyperplasia	0%	3.8%
Proliferative endometrium	25%	10.5%
Treatment rest and fibrosis	75%	85.7%

estrogen and progestogen action long-term on the endometrium. The risk factors for endometrial hyperplasia and endometrial cancer are summarised in Table 2.

Therefore, irregular menses (corpus luteum dysfunction), chronic anovulation (for instance PCOS); nulliparity (lack of 9 month progesterone dominant condition), estrogen-producing tumor or prolonged estrogen treatment unopposed by progestogens, are clinical risk situations. Decreased risk is associated with full-term pregnancy or estrogen/progestogen combination treatment (Table 3).

Therefore, significant risk reduction could be demonstrated by comparing multiparous with nulliparous women (RR 0.11; 95% C.I.; 0.04–0.34), hormonal contraceptives as estrogen/progestogen combination (RR 0.36; 95% C.I., 0.14–0.90) and lack of estrogen stimulation for more than 8 years (RR 0.23; 95% C.I.; 0.08–0.35).

There is a high association between body weight, diabetes mellitus and endometrial cancer [1].

Body weight	Diabetes mellitus
Overweight (BMI 28.0–29.9)	Diabetes mellitus type II
RR 1.5; 95% C.I. 1.1–2.1	RR 1.5; 95% C.I. 1.0–2.1
Obesity (BMI 30.0–33.9)	Diabetes mellitus type I
RR 2.9; 95% C.I. 2.2–2.4	RR 13.3; 95% C.I. 3.1–56.4
Excessive obesity (BMI > 34)	
RR 6.3; 95% C.I. 4.2–9.5	

Women with fertility problems have a higher risk to develop endometrial cancer (RR 4.6–9.7). One further aspect seems to be of interest: This is the association of ovarian volume and endometrial cancer risk:

(1) Increased ovarian volume is associated with higher estradiol concentration (p-trend = 0.007).
(2) Increased ovarian volume is associated with higher biological active free estradiol (p-trend = 0.005).
(3) Increased ovarian volume is associated with early menarche.

Indeed women with endometrial cancer have increased ovarian volume and higher estradiol levels [2].

There is elevated risk for endometrial hyperplasia and endometrial cancer with early menarche, particularly among premenopausal women with late menopausal age. This risk of endometrial cancer is decreasing with increasing age at menarche (p for trend = 0.004).

Both complete and incomplete pregnancy confer a protective effect against endometrial cancer and the proliferative effect increases with the total number of pregnancies (p for trend = 0.01). The protective effect of pregnancy on endometrial cancer risk remains unchanged with increasing time since last pregnancy [3]. The risk also decreases with increasing age at life birth (p for trend = 0.03) [4].

The protective effect of progestogen regarding endometrial hyperplasia and endometrial cancer besides the progestogen effect is the antiestrogen effect. Progestogens act as antiestrogen by reducing the estrogen receptor content and the ability to produce new estrogen receptor and inhibition of the increased conversion of estradiol the biologically less active estrone.

Progesterone produces a variety of responses in the target tissue endometrium depending upon which progesterone receptor type (A or B) is expressed by the tissue and the number of progesterone receptors present. A greater response is seen, of there is an abundance of Beta-type receptors. The close regulation of progestogen response determines the extent of response [5].

For abnormal endometrial development enzymes such as sulfase seems to be involved, which converts estrone sulfate to estrone and opens up the possibility for an increased conversion of estrone to estradiol. Progesterone reduces sulfatase activity and stimulates sulfate transferase and by this counteracts or prevents the increased availability of estrogens.

All this together underlines the inhibitory effect of progestogens on abnormal endometrial tissue growth [6].

The long lasting risk reduction by oral hormonal contraceptives (estrogen/progestogen combination) increases with the length of use and progestogenic potency.

Progestogen with high progestogenic potency [7]: RR 0.2; 95% C.I. 0.1–0.43.
Progestogen with low progestogenic potency: RR 0.39; 95% C.I. 0.25–0.60.

Estrogen users versus nonusers have an increased endometrial cancer risk (RR 2.3). Prolongation of use for 10 years and more results in a significant risk increase (RR 9.5).

This increased risk remains elevated 5 years or more after the discontinuation of the estrogen monotherapy (RR 2.3).

Interruption of the estrogen for 5–7 days per month was not associated with a lower risk compared to daily use. Also the endometrial cancer death risk among estrogen users was elevated (RR 2.7) [8]. In other studies the risk remained elevated more than 10 years off estrogen (RR 1.5; 95% C.I. 1.0–2.13) [9]. Women using combined estrogen/progestogen replacement therapy versus unopposed estrogen treatment had a higher risk reduction of endometrial cancer (RR 0.2; 95% C.I. 0.1–0.6) [10]. In women with estrogen monotherapy the addition of cyclic progestogen for at least 10 days per cycle decreased the risk of endometrial cancer by 50% compared to women, who had only stopped the estrogen treatment (RR 0.5; 95% C.I. 0.3–1.1) [11].