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SCIENCE DIRECT
Journal of Steroid Biochemistry & Molecular Biology 97 (2005) 441–450
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Pregnancy, progesterone and progestins in relation to breast cancer risk☆

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Abstract

In the last two decades the prevailing opinion, supported by the "estrogen augmented by progesterone" hypothesis, has been that progesterone contributes to the development of breast cancer (BC). Support for this opinion was provided by the finding that some synthetic progestins, when added to estrogen in hormone replacement therapy (HRT) for menopausal complaints, increase the BC risk more than estrogen alone. However, recent findings suggest that both the production of progesterone during pregnancy and the progesterone endogenously produced or exogenously administered outside pregnancy, does not increase BC risk, and could even be protective. The increased BC risk found with the addition of synthetic progestins to estrogen in HRT seems in all likehood due to the fact that these progestins (medroxyprogesterone acetate and 19-nortestosterone-derivatives) are endowed with some non-progesterone-like effects which can potentiate the proliferative action of estrogens. The use of progestational agents in pregnancy, for example to prevent preterm birth, does not cause concern in relation to BC risk.

Keywords: Breast cancer; Pregnancy; Progesterone; Progestins

1. Introduction

It is generally accepted that female sex hormones are linked to the etiopathogenesis of breast cancer (BC) [1]. In vitro studies have established that estrogens markedly increase the mitotic rate of both normal and malignant breast epithelium cells; there is also evidence that estradiol and its metabolites are carcinogenic to human breast epithelium [2,3]. Conversely, the picture is more complex for progesterone, which may affect mitotic activity of normal and malignant breast cells by various mechanisms and may have proliferative or anti-proliferative (anti-estrogenic) effects depending on the individual study parameters [4–7].

In spite of this uncertainty, the prevailing opinion in the last two decades, supported by the "estrogen augmented by progesterone" hypothesis [1], is that progesterone produced during the ovarian cycle contributes to the development of BC. An important endorsement of this opinion was provided by the finding that some synthetic progestins, when added to estrogen in hormone replacement therapy (HRT) for menopausal complaints, increase the BC risk much more than estrogen alone [8–10]. However, recent findings suggest that both the production of progesterone during pregnancy and the progesterone endogenously produced or exogenously administered outside pregnancy, do not increase the risk, and could even be protective.

The aim of this paper is to review and discuss the available data on these topics of undoubted relevance from a clinical point of view.

2. Pregnancy and subsequent breast cancer risk

2.1. Epidemiological findings

Pregnancy, and especially first pregnancy, has an important influence on subsequent BC risk [11,12]. A first pregnancy completed prior to age 30 is associated with opposing influences on BC risk, with a transient 3–4 years of increased risk and beneficial effects over the long term [11,12]. In

☆ Presented at the European Progestin Club Scientific Meeting, Amsterdam, The Netherlands, 05 October, 2004.

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doi:10.1016/j.jsbmb.2005.08.015

Table 1
Preeclampsia in first pregnancy and risk of subsequent breast cancer

Study	Relative risk [95% C.I.]
[14]	0.81 [0.56–1.20]
[15]	0.81 [0.71–0.91]
[12]	0.85 [0.65–1.12]
Age at first birth	
>30 years	0.33 [0.16–0.65]
≤30 years	0.93 [0.66–1.32]
Years since first birth	
<4 years	0.21 [0.05–0.91]
≥4 years	0.86 [0.62–1.18]

contrast, late first pregnancy increases both short- and long-term risk. For instance, in a prospective study of a cohort of 694,657 parous women, if the age at first birth was 30–34 or >35 years, the risk was 48% (95% C.I.: 31–66%) or 56% (95% C.I.: 33–82%) greater than in women with first birth at <30 years of age [13].

Characteristics of pregnancies, especially first pregnancy, also influence subsequent BC risk. For instance, preeclampsia is associated with a reduction in the risk [12,14,15], which is especially relevant in the first 4 years after the birth and in women aged >30 years of age at first birth [12] (Table 1). Interestingly, BC risk is markedly reduced in women whose mothers had preclampsia [16]. Independent from preeclampsia, women with pregnancies with reduced placental size and function show a reduction in BC risk, this being especially relevant in women of older age at first pregnancy [17].

Duration of pregnancy also has a strong influence on the subsequent BC risk. In contrast to a number of previous reports [11], induced or spontaneous abortion does not seem to increase the risk [18–20]; however, first pregnancies that are spontaneously or intentionally interrupted in early gestation do not provide protection against BC [18]. In general, the reduction of BC risk is related to the length of gestation. Studies on preterm deliveries show a clear increase in risk in women with a gestation period under 32 weeks, with a decrease in risk with increasing duration of gestation [12,13,21] (Table 2). Interestingly, premature birth also seems to result in an increased BC risk in the offspring [22]. The protective effect of a delivery at more than 32 weeks—and/or the deleterious effect of a delivery at less than 32 weeks—can be observed especially in first pregnancy [12,21], but also in further pregnancies [21], and could be particularly relevant when the age at delivery is more than 30 years [21] (Table 2).

Summing up, pregnancy, depending on its characteristics (length of gestation, placental function), can have either a negative or a protective effect on the subsequent risk:

- both the effects seem to be substantially lacking in the first trimester, as suggested by the findings associated with spontaneous or induced abortion;
- the negative effect seems to prevail during the second trimester and the first part of the last trimester, as indicated by the deleterious consequences of a delivery before 32 weeks;
- the negative effect is reduced and/or the protective effect is increased in the case of altered placental function (preeclampsia, reduced placental size independent of preeclampsia, etc.);
- the protective effect prevails strongly during the second part of the last trimester, probably reducing the short-term risk and certainly causing the long-term beneficial effects, as suggested by the findings referring to pregnancies with a delivery at term.

2.2. *Factors involved in the effects of pregnancy on the subsequent BC risk*

Pregnancy can affect breast tissue and the subsequent BC risk through different (hormonal, metabolic, immunological) mechanisms [11]. However, great importance is attributed to the histological and functional modifications induced in breast epithelial tissue by the dramatic increases in many hormones.

2.2.1. *Breast epithelial tissue modifications during pregnancy and their effects on subsequent BC risk*

Breast tissue modifications during pregnancy have been excellently described by Russo and Russo [23,24]. The modifications occur in two distinct dominant phases characteristic of the early and late stages of pregnancy. The early stage is

Table 2
Relative risk of subsequent breast cancer according to gestational age at delivery

Study	Gestational age (weeks)	RR [95% C.I.]	
[21]	>35	1	
	35–34	1.08 [0.71–1.66]	
	33–32	1.12 [0.62–2.04]	
	31–29	2.08 [1.20–3.60]	
	<29	2.11 [1.00–4.45]	$p = 0.04$
Nulliparous	>37	1	
	36–32	1.14 [0.70–1.87]	
	<32	2.41 [1.07–5.42]	
1+ previous pregnancies	>37	1	
	36–32	1.03 [0.76–1.39]	
	<32	1.94 [1.14–3.29]	
<30 years at delivery	>37	1	
	36–32	1.20 [0.77–1.89]	
	<32	1.62 [0.60–4.33]	
>30 years at delivery	>37	1	
	36–32	1.06 [0.73–1.37]	
	<32	2.33 [1.35–3.64]	
[13]	>36	1	
First pregnancy	36–32	1.11 [0.97–1.19]	
	<32	1.22 [0.97–1.53]	$p = 0.02$
[12]	>36	1	
First pregnancy	36–32	0.93 [0.73–1.14]	
	<32	2.14 [1.16–3.90]	$p = 0.03$

characterized by growth consisting of proliferation of the distal elements of the ductal tree. The epithelial cells not only increase in number due to active cell division, but they also increase in size mainly because of cytoplasm enlargement. In the middle of pregnancy, the lobules are further enlarged and increased in numbers, and show evidence of early secretory activity. The mammary changes that characterize the second half of pregnancy are chiefly continuation and accentuation of the secretory activity. The formation of true secreting units or acini, the differentiated structures, becomes increasingly evident, while proliferation of new acini is reduced to a minimum. The secretory acinus formed in the last stage of pregnancy is a terminal outgrowth that marks the end of glandular differentiation. After delivery, in the lactational and post-lactational stages, breast epithelium shows a series of involutional and regressive changes [23].

Factors that cause the extensive proliferation of breast cells during pregnancy could also trigger the proliferation of existing tumor cells, leading to the transient increased risk of BC shortly after pregnancy [25]. This could be particularly relevant among older primparas, who are more likely to have preneoplastic breast lesions or occult neoplasm [12]. Conversely, the terminal differentiation that occurs late in pregnancy has a protective effect and causes a reduction in the susceptibility of breast tissue to malignant transformation in the long term [11,12,25]. This explains the lifetime protection against the development of BC by an early full-term pregnancy (half the risk compared with nulliparous women) [26]. Actually, the differentiation process that characterizes term-pregnancy causes persistent morphological and functional changes in mammary gland tissue, with decreased steady state proliferative activity [23,26]. Conversely, as mammary cells proliferate during the first and second trimester and differentiate in the third trimester, termination of pregnancy due to pre-term delivery, prior to full differentiation of mammary stem cells, may increase the susceptibility of the breast to neoplasia, as suggested by epidemiological findings [12].

2.2.2. *Hormonal factors that affect breast tissue modifications and subsequent BC risk*

Besides sex hormones, other hormones whose production is increased during pregnancy could affect breast tissue modifications and subsequent BC risk. For instance, insulin-like growth factor-I (IGF-I) and other mitogens may stimulate proliferation of mammary cells and thereby facilitate both the initiation and the promotion of BC [12]. In contrast, chorionic gonadotropin (hCG) may protect against the subsequent development of BC by promoting apoptosis, fostering differentiation, and inhibiting proliferative growth [12,24], while alpha-feto-protein (AFP) has been shown to inhibit, as well as enhance, proliferative growth [12,27]. However, the effects of sex hormones, estrogens and progesterone, are well recognized [11,25].

The levels of circulating estrogens and progesterone increase with advancing gestational age, thus the breast is exposed to the highest concentrations of these hormones during the third trimester of pregnancy [11,25]. In particular, progesterone production rates and plasma concentrations show a sharp increase in the last weeks of gestation [11] (Fig. 1). During pregnancy, estrogens stimulate proliferation and ductal growth, whereas high concentrations of progesterone induce lobular-alveolar development and differentiation [25], i.e. potentially protective effects.

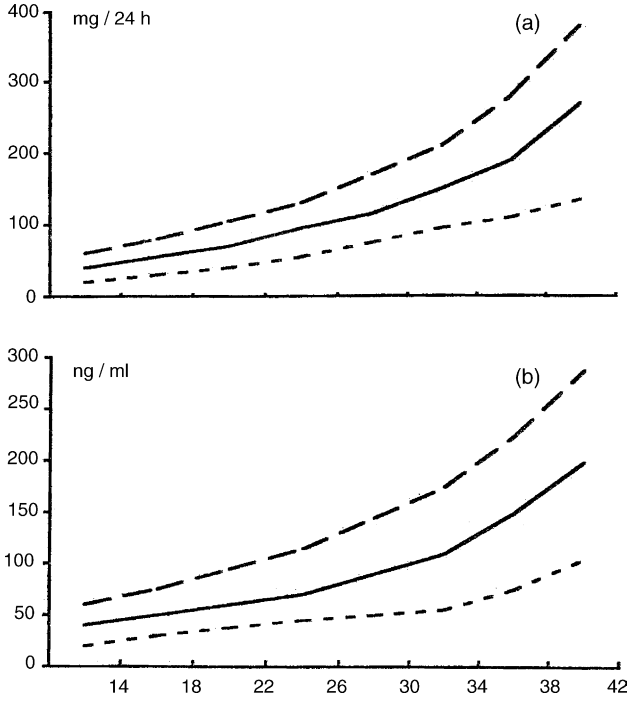

Fig. 1. Progesterone production rates (a) and plasma concentration (b) during pregnancy (from [11]; with permission).

In a prospective study of the influence of steroid hormone levels in the third trimester of pregnancy on subsequent BC risk, increasing progesterone levels were associated with a lower incidence of BC [25] (Table 3). This relationship was stronger for BC diagnosed at or before age 50. The same study showed that women with the lowest estrone and estriol levels tended to have a reduced risk, especially among cases diagnosed after age 50, whereas higher concentrations of total estrogens relative to progesterone were associated with an increased incidence of BC; women in the highest quartile of the total estrogens/progesterone ratio showed an odds ratio of

Table 3
Odds ratios (ORs) for the incidence of breast cancer associated with third-trimester serum progesterone levels [25]

Progesterone (ng/ml)	ORs [95% C.I.]		
		Age at diagnosis	
		<50 years	>50 years
<124.25	1	1	1
124.25 to <197.11	0.66 [0.38–1.2]	0.54 [0.27–1.1]	0.86 [0.40–1.9]
197.11 to <269.97	0.57 [0.30–1.1]	0.41 [0.18–0.9]	0.79 [0.34–1.8]
≥269.97	0.49 [0.22–1.1]	0.30 [0.10–0.9]	0.87 [0.31–2.5]
p-trend	0.08	0.04	0.86

Table 4
Reported levels of key hormones in pregnancies with preeclampsia compared with those without preeclampsia

Progesterone	Increased	[28,29]
Estrogens	Reduced/ normal	[28,30]
Androgens	Increased	[28,30,33,34]
Human chorionic gonadotropin	Increased	[28,35–37]
α-Fetoprotein	Increased	[37,38]
Insulin-like growth factor-I	Reduced	[28,31,32]
Insulin-like growth factor binding protein-1	Increased	[28,31]

2.0 (95% C.I.: 0.87–4.7) compared with women in the lowest quartile ($p = 0.06$) [25].

Progesterone levels are reported to be increased in preclamptic pregnancies [28,29], which are associated with a reduction in subsequent BC, particularly in older primiparas and in the first few years following delivery [12] (Table 1). However, relative to normal pregnancies, those complicated by preclampsia are also typified by decreased levels of estrogens [28,30] and IGF-I [28,31,32], and by elevated levels of androgens [28,30,33,34], IGF binding protein-1 [28,31], hCG [28,35–37] and AFP [37,38] (Table 4). All these factors may act both individually and synergistically to decrease BC risk by reducing proliferative growth of mammary tissue and by inhibiting the malignant transformation of precancerous lesions or the promotion of occult neoplasms [12].

Low progesterone levels and/or a reduced progesterone/estrogen ratio have been shown in some studies, but not others [39–41], in pregnancies with preterm delivery, which are associated with increased BC risk (Table 2). Most importantly, progesterone seems to have a predominant role in promoting the process of glandular differentiation in the last weeks of pregnancy and consequently in having the protective effect shown in full-term pregnancies (Table 2). In fact, progesterone, among the potentially protective hormones, is the only one that shows a sharp increase in the last weeks of gestation [11,42] (Table 5) (Fig. 1).

Overall, the available data suggest that progesterone during pregnancy has a protective influence on the subsequent BC risk.

Table 5
Key modifications in hormone plasma levels during normal pregnancy [11,42]

Estrogens	Progressive increase until term, with accelerated rate of increase at 35–36 weeks
Progesterone	Slow progressive increase in the first 30 weeks; sharp increase in the final weeks
Human chorionic gonadotropin	Maximal level of about 100,000 IU/L at 8–10 weeks; decrease to about 10–20,000 IU/L by 10–20 weeks
α-Fetoprotein	Increase until week 32, followed by a decrease
Insulin-like growth factor-1	Increase by the thrid trimester

3. Progesterone outside pregnancy and breast cancer risk

3.1. Endogenous progesterone

The main evidence advanced in support of the "estrogen augmented by progesterone" hypothesis is the finding that proliferation of breast epithelium increases in the luteal phase of the menstrual cycle, when the ovaries produce both estradiol and progesterone, reaching a peak 9–10 days after ovulation [43–46]. The increase in proliferation occurs particularly in the terminal duct lobular unit (TDLU) [43,44,46] where most breast carcinomas arise [47]. However, it has not been established that the luteal phase cell proliferation peak is due to progesterone. An alternative hypothesis is that it is only estrogen that stimulate the proliferation of breast epithelium, but that there is a lag of 4–5 days between the estrogen peak and the proliferation peak [45,48]. In fact, breast epithelium does not appear as sensitive an estrogen target organ as the endometrium, probably because estrogens have an indirect effect on proliferation that requires paracrine factors to mediate their signal [48]. It is noteworthy that studies on intact normal human breast tissue grafted subcutaneously to athymic nude mice found that estrogen, not progesterone, is the major epithelial cell mitogen [48,49]. Evidence that progesterone may in fact reduce estrogen-induced breast proliferation comes from a study in which gels containing estradiol or progesterone, or a combination of both, were applied daily to the breasts of postmenopausal women for 14 days prior to surgery (not for malignancy) [50]. Importantly, histological studies show that the number of apoptotic breast cells also starts increasing a few days after ovulation (after the mitosis rate has already started increasing), reaching a peak just before menstruation [43].

The 'estrogen augmented by progesterone' hypothesis was also motivated by the following epidemiological observations in premenopausal women: reduced risk of BC in women with oligomenorrhea, in particular those who have had menstrual irregularities for prolonged periods after menarche, probably because of persistent lack of ovulation [51]; reduced risk of BC in obese premenopausal women, probably in relation to fewer ovulations [52]; and greater BC risk in women with short menstrual cycles, implying greater cumulative time in the luteal phase since cycle length varies mainly because the follicular phase varies [45,53]. Note, however, that oligomenorrhea implies not only less progesterone but also fewer estradiol peaks and less cumulative estrogenic stimulation, while short cycles are either ovulatory, implying greater cumulative exposure to estradiol, or are anovulatory, implying reduced exposure to progesterone.

That normal or marked progesterone production in premenopausal women may even be protective against BC was suggested by the results of a prospective study in a cohort of 5963 premenopausal women in whom blood sampling was carefully timed in the luteal phase [53]: women in the highest tertile of progesterone showed a highly significant

Table 6
Relative risk of premenopausal breast cancer by serum mid-luteal progesterone level; based on 40 case women and 108 matched controls with regular menses [53]

	Serum progesterone concentration (tertiles)			
	Low	Middle	High	
Progesterone (ng/ml)	<9.01	9.01–13.54	>13.54	
Relative risk[a]	1	0.90 [0.38–2.13]	0.32 [0.10–1.06]	$p = 0.086$
Relative risk[b]	1	0.40 [0.13–1.20]	0.12 [0.03–0.52]	$p = 0.005$

[a] Adjusted by age and body mass index.
[b] Adjusted by age, body mass index, time from sampling to next menses, length of the cycle in which blood was sampled, LH, FSH.

decrease in BC risk compared with women in the lowest tertile (RR: 0.12 [0.03–0.52]; $p = 0.005$) (Table 6). Several previous case–control studies have suggested similar conclusions [54–58].

3.2. Progestins/progesterone in hormone replacement therapy

The progestins mainly employed in HRT are synthetic compounds endowed with progesterone-like action on the endometrium, but are somewhat different from natural progesterone.

In the US, the most commonly used progestin by far is medroxyprogesterone acetate (MPA); generally, MPA is combined with conjugated equine estrogens (CEE) in formulations for oral administration [59] in a sequential regimen or, more recently, in a continuous-combined regimen [60,61]. In the UK, where oral or transdermal estradiol, as well as CEE, are used, the progestins are mainly 19-nortestosterone-derivatives (norethisterone acetate, norgestrel and levonorgestrel), with only about 20% of treated women using MPA [62]. In northern Europe, 19-nortestosterone-derivatives are mainly combined with oral estradiol, both in sequential and continuous-combined formulations, while MPA is used by less than 20% of treated women, in sequential formulations [63–65]. In contrast, in central and southern Europe, both 19-nortestosterone-derivatives and a range of progesterone-derivatives are used, and these are added to various types of estrogens. France is unusual in that there is widespread use of micronized progesterone (mainly oral) in combination with oral or transdermal estradiol [66].

3.2.1. Epidemiological findings

The BC risk associated with the use of estrogen alone, or estrogen plus progestin, has been addressed in two randomized studies performed in the US, and in a number of observational studies conducted in the US, UK and northern-European countries. Both controlled studies and most observational studies suggest that the addition of synthetic progestins to estrogen in HRT, particularly in a continuous-combined regimen, increases the BC risk compared with estrogen alone [67]. Risk differences between sequential and continuous-combined regimens seemed more marked and consistent in studies conducted in northern European countries than in those conducted in the US [67]. This might be due to the fact that, in northern Europe, the daily dose of 19-nortestosterone-derived progestins (most often norethisterone acetate, 1 mg) is the same in both continuous-combined and sequential regimens, so that the monthly cumulative dose in the former is twice that in the latter, while in the US, the daily MPA dose in combined regimens is much lower (2.5 mg) than in sequential regimens (5–10 mg), so that cumulative dose does not differ greatly between them.

It is important to realize that recent findings relating to the use of natural progesterone, in sharp contrast to those referring to the use of progestins, are reassuring. These findings come from a cohort study carried out in France, where oral micronized progesterone has been used in cyclic regimens of HRT by large numbers of menopausal women for over two decades. In this study, based on the E3N-EPIC cohort that included 54,548 postmenopausal teachers who had not taken any HRT before enrolment and who were followed up for an average of 5.8 ± 2.4 years, oral micronized progesterone, in contrast to synthetic progestins, did not increase BC risk in women treated with transdermal estradiol [66]. The relative risks, compared with untreated women were: 1.2 (95% C.I.: 0.8–1.8) for transdermal estradiol alone; 0.9 (95% C.I.: 0.7–1.2) for transdermal estradiol with micronized progesterone and 1.4 (95% C.I.: 1.2–1.7) for transdermal estradiol with synthetic progestins (Table 7).

As we have discussed previously, the evidence adduced in favour of the 'estrogen augmented by progesterone' hypothesis is open to different interpretations; conversely, available data show that the physiological production of progesterone during the menstrual cycle may be associated with a lower risk of BC. The lack of increase in BC risk with cyclical HRT regimens containing natural progesterone, as found in the E3N-EPIC study [66], is therefore biologically plausible. It is probable that the increase in BC risk found in other studies with HRT is related to the fact that synthetic progestins, rather than progesterone, were used.

3.2.2. Differences between some progestins and progesterone

All the studies showing an increased risk following the addition of progestin to estrogen have been conducted in the US, UK or northern-European countries. The progestins predominantly used in these countries have activities that do not completely coincide with those of progesterone.

Table 7
Relative risk of breast cancer associated with use of transdermal estradiol alone or combined with micronized progesterone or synthetic progestins by menopausal women with incident hormone exposure (E3N-EPIC Cohort) [66]

Multivariate-adjusted relative risk [95% C.I.]

	Transdermal estradiol	Transdermal estradiol + micronized progesterone	Transdermal estradiol + progestins
Overall	1.2 [0.8–1.7]	0.9 [0.7–1.2]	1.4 [1.2–1.7]
Duration of exposure			
<2 years	1.4 [0.8–2.2]	0.9 [0.6–1.4]	1.6 [1.3–2.0]
2–4 years	1.4 [0.7–2.6]	0.7 [0.4–1.2]	1.4 [1.0–1.8]
>4 years	0.3 [0.1–1.8]	1.2 [0.7–2.0]	1.2 [0.8–1.7]

In northern European countries and in the UK, the use of 19-nortestosterone-derivatives (norethisterone acetate, norgestrel, levonorgestrel) that have androgenic activity [68,69] prevails, while in the US, the predominant progestin is MPA, which is also endowed with androgenic properties although to a lesser extent [69,70]. The increased BC risk found with the use of these progestins might be related to their 'non-progesterone' activities.

In fact, these progestins differ from progesterone because they can have direct effects on normal and malignant breast cells, and particularly because of indirect effects (metabolic and hepatocellular) that could stimulate BC cells in synergy with estrogens or increase estrogen bioavailability (Table 8).

In vitro studies have shown that progestins derived from 19-nortestosterone interact with estrogen receptors [71] and exert an estrogen-like proliferative effect on BC cell lines [72,73].

While in vitro studies indicate that progestins decrease the formation of estradiol in BC cells by inhibiting the activity of estrone sulfatase and influencing the activities of 17β-hydroxysteroid dehydrogenases [17β-HSD] [74], MPA could differ from progesterone and other progestins in being able to promote the reductive transformation of estrone into estradiol via 17β-HSD [74,75]. Such an effect might be important in women with high circulating levels of estrone, as occurs when taking oral HRT [75].

Table 8
Breast cancer risk: properties of some progestins

Estrogenic activity [71–73]	19-Nortestosterone derivatives
Influence on the enzyme that reduces estrone to estradiol in cancer cells [74–75]	Possibly MPA
Metabolic effects (opposing those of estrogen) on insulin sensitivity [95,96,100–102]	Particularly the 19-nortestosterone derivatives, but also MPA
Hepatocellular effects (opposing those of estrogen)	Particularly the 19-nortestosterone derivatives, but also MPA
Increase in IGF-I level [98,103–105]	
Decrease in SHBG level [91,103,105]	
Binding to SHBG, with further reduction in capacity to bind estrogens [68]	19-nortestosterone derivatives

MPA: medroxyprogesterone acetate; IGF-1: insulin-like growth factor-1; SHBG: sex hormone binding globulin.

Insulin resistance, hyperinsulinemia and high blood glucose are associated with an increased risk of BC [76–81]. Elevated levels of insulin can directly stimulate the proliferation of cancer cells, an action probably mediated by the IGF-I receptor. High insulin may also have indirect actions, by increasing liver production of IGF-I, decreasing some IGF-binding proteins and sex hormone binding globulin (SHBG), and stimulating the ovarian production of androgens [76]. A randomized controlled study of dietary intervention in menopausal women showed that an insulin-lowering diet can reduce the bioavailability of sex hormones and IGF-I [82,83]. Circulating IGF-I derives mainly from the liver; its production is stimulated by growth hormone and facilitated by an affluent nutritional status, particularly by a high consumption of protein, and by insulin level [84]. IGF-I bioavailability is regulated by IGF binding proteins (IGFBP), also produced in the liver. Levels of IGFBP-1 and IGFBP-2, which decrease IGF-I bioavailability, correlate inversely with blood insulin levels [85]. IGF-I has potent mitogenic and anti-apoptotic effects on BC cells. The mitogenic effect is synergistic with that of estrogens [86,87]. As recently reviewed [88,89], most prospective studies indicate that high IGF-I levels in premenopausal women (i.e. women still producing estrogens) are a risk factor for later development of BC. Furthermore, one prospective study found a relationship between IGF-I levels and BC risk in menopausal women taking HRT [90]. SHBG is also produced by the liver, and its production is inhibited by insulin and IGF-I [76]. It specifically binds testosterone and, with lower affinity, estradiol. Moreover, through a specific receptor on the membrane of estrogen-sensitive BC cells, SHBG could have an anti-estrogenic, antiproliferative effect [91,92]. Low SHBG levels are a risk factor for BC in postmenopausal women [91] and possibly also in premenopausal women [53]. Overall, these data indicate that metabolic and hepatocellular factors play a crucial role in augmenting the effect of estrogen on breast tissue and on BC cells.

Estrogens, particularly orally administered estrogens, are able to counteract metabolic and hepatocellular factors that increase the risk of BC. One way they do this is by increasing insulin sensitivity and hence lowering circulating insulin levels [93–96]. Oral estrogens, through their hepatocellular actions (accentuated by the first pass effect), also induce a

significant reduction in circulating IGF-I and a sharp increase in circulating SHBG [91,93,97]. Estrogens also increase circulating IGFBP-1 levels, again by a direct effect on liver cells, and this may further reduce the activity of circulating IGF-I [98]. Most likely the above mentioned metabolic consequences of oral estrogens are more important in women with high metabolic risk, namely obese women; this would explain why BC risk decreased in the CEE only arm of the WHI study [99]

Depending on their degree of androgenicity, androgenic progestins reduce insulin sensitivity, opposing the action of estrogens [95,96,100–102]. Moreover, particularly when taken orally, androgenic progestins (e.g. norethisterone acetate and, to a lesser extent, MPA) provoke an increase in circulating IGF-I thus opposing the action of estrogens [98,103–105]. These progestins also oppose the increase in IGFBP-1 caused by oral estrogens, and this effect probably contributes to the increase in IGF-I activity [98]. Androgenic progestins, and to a much lesser extent MPA, also oppose the estrogen-induced increase in SHBG secretion by the liver [91,103,105]. In contrast, progestins with progesterone-like activity only, like dydrogesterone, have essentially no metabolic and hepatocellular effects and do not affect circulating IGF-I and SHBG levels [94,97,98,103–106].

Overall, the available data suggest that androgenic progestins increase BC risk through non-progesterone-like effects.

4. Conclusion

Available data suggest that progesterone produced during pregnancy does not have deleterious effects on BC risk; conversely, it could have a predominant role in the long term protective effect against BC shown by full-term pregnancies.

Even outside pregnancy, the balance of the in vivo evidence is that progesterone does not have a cancer-promoting effect on breast tissue. The greater BC risk related to the use of HRT preparations containing estrogen and synthetic progestins seems in all likelihood to be due to the fact that many of the progestins used have several non-progesterone like actions that potentiate the proliferative effect of estrogens on breast tissue and estrogen-sensitive cancer cells. Particularly relevant seem to be the metabolic and hepatocellular effects (decreased insulin sensitivity, increased levels and activity of IGF-I, and decreased levels of SHBG), which oppose the opposite effects induced by oral estrogen.

The use of progestational agents in pregnancy, e.g. to prevent preterm birth [107,108], does not cause concern in relation to BC risk. On the contrary, progestational agents could even be protective, especially when they succeed in avoiding preterm delivery, a well documented risk factor for the subsequent development of BC.

Acknowledgements

The authors would like to thank Prof. Franco Berrino, Dept. of Preventive and Predictive Medicine, Istituto Nazionale dei Tumori, Milano, for his precious suggestions and kind support, and Ms. Saveria Battaglia for her skilled secretarial work.

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