Review Article Open Access
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Archives Of Breast Cancer

DOI: 10.19187/abc.201964150-155

# Miscellaneous Exogenous Hormones and Breast Diseases: A Matter of Concern for the Gynecologist

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ARTICLE INFO

**Received:**
09 October 2019
**Revised:**
27 October 2019
**Accepted:**
02 November 2019

**Key words:**
Breast Cancer,
Finasteride,
Implant,
Intrauterine device,
Medroxyprogesterone,
Spironolactone.

ABSTRACT

**Background:** The effect of exogenous sex hormones on the risk of breast cancer has been shown for some compounds but for other compounds it is under detailed investigation. This study, as part of a quadruple of articles reviewing the consequences of using sex hormones in women with various breast conditions, discusses the prescription of non-oral hormonal contraceptives and miscellaneous exogenous steroid hormones.

**Method:** We browsed international clinical guidelines and carried out a comprehensive search in the literature by relevant keywords in order to extract data about the effects of hormone-releasing intrauterine devices, injectable depot-medroxyprogesterone acetate, contraceptive implants, cyproterone acetate, finasteride, and spironolactone on the breast.

**Results:** Studies are scarce for most of these compounds, and information comes mainly from researches about oral contraceptives and hormone replacement therapy. Although none is recommended for use in patients with breast cancer, administration in benign disorders of the breast, women with positive family history of breast cancer and general women is acceptable with minor risks.

**Conclusions:** Most non-oral hormonal methods of contraception and miscellaneous available hormone compounds prescribed for the treatment of hormonal disorders are safe for temporary use, except for women with breast cancer. For them, analogues of gonadotropin-releasing hormones may be considered a safe hormonal prescription.

## Introduction

Because of the association of breast cancer with female sex hormones[1-6], prescribing hormonal combinations in women especially in those harboring a disorder in the breast usually goes with hesitation and uncertainty. In order to answer some questions that physicians have in this regard, four sequential articles have been written discussing the prescription of different hormonal compounds in various conditions regarding the breasts. The first[7] and second[8] parts scrutinized the effects of hormone replacement therapy (HRT) and oral contraceptive pills (OCP) on the breasts, respectively. In this third article, our approach is to non-oral hormonal contraceptives and to hormones that are usually prescribed in various hormone-related disorders for non-HRT and non-contraceptive purposes. These have been rarely addressed worldwide and hardly regarded to have initiated malignant changes in the breast. Meanwhile, practitioners who specialize on breast diseases are usually consulted about them by their colleagues. Therefore, in this section, we will discuss the effects of levonorgestrel-releasing IUDs (LNG-IUDs), injectable depot-medroxyprogesterone

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acetate (DMPA), progesterone implants, cyproterone acetate, finasteride and spironolactone.

**Methods**

We aimed to find valid data about the effects of miscellaneous hormones on the breasts. Because of interesting relevant literature about the effects on male breasts, we also searched and entered related data. We carried out a comprehensive search in Google Scholar and PubMed by using combinations of these keywords: "benign breast", "breast cancer", "conjugated estrogen", cyproterone, "ethinyl estradiol", etonogestrel, fibroadenoma, fibrocystic, finasteride, levonorgestrel, "male breast", medroxyprogesterone, and "progesterone implant". We extracted data from all pertinent works including cohort studies, clinical trials and reviews. We also browsed valid clinical guidelines including the International Agency for Research on Cancer (IARC), Monographs on the Evaluation of Carcinogenic Risks to Humans, the guidelines of the Society of Family Planning (SFP), the US Medical Eligibility Criteria for Contraceptive Use by the Centers for Disease Control and Prevention (CDC), and the US Selected Practice Recommendations for Contraceptive Use. All pertinent information was extracted from these references.

**Results and Discussion**

*Depot-medroxyprogesterone acetate*

The approval of the injectable form of depot-medroxyprogesterone acetate (DMPA) as a contraceptive method has taken a long gradual course from its synthesis in 1963 to its use in more than 100 countries now[9]. This lag was partly due to the probability of increasing the risk of breast cancer, which is still a matter of debate. However, while some studies have shown an approximate 2.2-fold increased risk of breast cancer due to DMPA [10,11], this association was shown to stop after discontinuation of the hormone, or not to existo.[11-14] Thus, in addition to the general population, contraception using DMPA is permitted in women with benign breast disorders and even in those with psitive family history (FH) of breast cancer. Nevertheless, its use is contraindicated in patients with breast cancer, and considering the theoretical hazards, in survivors of the disease.[15,16]

*Progesterone Releasing Intrauterine Devices*

Intrauterine devices (IUDs) are used for long-acting reversible contraception (LARC). Some types of commonly-used IUDs are those that release Levonorgestrel, or LNG-IUDs.[15, 16] Despite the hormonal basis, levonorgestrel reaches very low levels in the serum of women who use these IUDs.[17]

Several large-scale studies have assessed the risk of breast cancer in women who use LNG-IUDs. They did not show an increased risk[18-21], except for one research derived from a Finnish registry which revealed an unexpectedly higher risk.[22] Therefore, according to SFP and CDC recommendations, LNG-IUDs should not be offered to women with present or previous breast cancer[15-17], with the probable exception of breast cancer survivors on tamoxifen, where LNG- IUDs might counteract proliferative effects of tamoxifen on the endometrium.[15, 16, 23-25] Use of these devices for contraception in women with benign diseases of the breasts and in patients with positive FH of breast cancer is recommended.

*Contraceptive implants*

One of the LARC methods consists of implanting flexible rods containing and gradually releasing progestins. These are easily planted under the skin of the arm or removed whenever needed. The etonogestrel implant is the most widely used method.[15,16,26,27]

Studies investigating the association of contraceptive implants with breast cancer risk are scarce. One study with a small sample size derived no increased risk[14], while an ethnic-based research showed a significant rise in the risk of breast cancer in users of progesterone implants.[28] Data of both studies should be considered with caution. Meanwhile, implants are not recommended as a method of contraception in breast cancer patients or survivors, while their use in benign breast disorders and women with positive FH is allowed.[15,16]

*Non-contraceptive, non-HRT exogenous oral estrogen and progesterone compounds*

Different formulations containing synthetic estrogens or progesterone, although mostly used as OCPs or for HRT, are sometimes used for the treatment of hormone-related conditions such as abnormal uterine bleeding, menstrual irregularity, endometriosis, or hirsutism. However, the effects on the risk of breast cancer and on benign breast diseases have not been studied specifically for this purpose. For example, medroxyprogesterone in the oral form as tablets, megestrol acetate and dydrogesterone are commonly used for the treatment of menstrual disorders. Megestrol acetate has been studied for this purpose in breast cancer survivors, and also as an appetite stimulator for reversing cachexia in patients with metastatic breast cancer. These works generally yielded positive results, but the effects on the prognosis of cancer have not been investigated.[29-34] The effects of dienogest on the breast tissue when consumed for the treatment of endometriosis have been explored in a study. All patients had significant decrease of breast size and improvement of mastopathic changes.[35]

Suggestions for the use of progesterone and estrogen compounds for the treatment of the mentioned gynecologic disorders in women with different breast conditions can be deducted from recommendations for OCPs as discussed in the first article of these series [8] and HRT as addressed in the second article [7]. They are demonstrated in table 1.

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**Table 1.** Suggestions for exogenous estrogen/progesterone use in different breast conditions

| Breast condition | OCP[8] | HRT[7] | Temporary use for treatment purpose |
|---|---|---|---|
| Normal | Yes | Yes | Yes |
| BBD | Yes | Yes: For low-risk lesions<br>No‡‖: For high-risk lesions† | Yes |
| Active breast cancer | No | No | No |
| BC Survivor | No | No | No |
| FH + | Yes | Yes ‖ | Yes‖ |
| BRCA + | Yes but non-hormonal methods preferred | No‡‖ | Yes‖ |

*like abnormal uterine bleeding, menstrual irregularity, endometriosis, hirsutism; †like atypical hyperplasia of the breast; ‡except for short-term, low-dose HRT in intractable cases; ‖ the patient must know about potential risks.
BBD= benign breast disorder, BC= breast cancer, FH= family history, HRT= hormone replacement therapy

It is interesting that while these compounds are considered to have stimulatory effects on hormone receptor-positive breast cancer, they paradoxically can have beneficial effects on advanced, hormone-resistant cases of breast cancer.[36-40]

*Cyproterone acetate*

Cyproterone acetate is a synthetic derivative of hydroxyprogesterone, which has a relatively high antiandrogenic as well as some antigonadotropic effects.[41, 42] It is usually used as part of the management of menstrual disorders and hirsutism, or contraception.[43] It has also been used in prostate cancer.[42, 44] One of its minor side effects is breast discomfort.[45]

While drugs with estrogenic or progestronic properties are sometimes administered in intractable advanced metastatic breast cancer in women, cyproterone acetate has not proved effective in this setting.[46] On the other hand, two studies have demonstrated beneficial effects for this compound in advanced cases of male breast cancer.[47,48]

Cyproterone acetate is occasionally administered alone for the management of menstrual issues or hirsutism, but probable adverse effects on breast cancer risk, and also on benign breast disorders have not been studied in that setting. Therefore, the same recommendations for progesterone-only oral contraceptive pills can be followed for this medicine too.[8]

*Finasteride*

Finasteride is an anti-androgen which functions by counteracting the action of 5αreductase. It is mostly used in the treatment of prostatic hyperplasia, androgenic alopecia in women, and sometimes in hirsutism.[43] While increased risk of male breast cancer has been attributed to finasteride in previous studies[49,50], this has not been confirmed in two recent works.[51, 52] Up to the present time, specific contraindication in women with breast disorders have not been defined.

*Spironolactone*

Spironolactone is an aldosterone antagonist with anti-androgenic effects that is commonly used for the treatment of hirsutism.[43] Although its potential for increasing male or female breast cancer has been put forward in earlier studies because of some case reports or series[53, 54], the association is not confirmed by other works.[55,56] Until now, specific contraindication in women with breast disorders have not been defined.

*Gonadotropin-releasing hormone Analogues*

Analogues of gonadotropin-releasing hormone (GnRH) bind competitively to central GnRH receptors in the pituitary gland. They are among the pharmacological treatments for the treatment of menorrhagia[57] and the premenstrual syndrome.[58,59]

One of the common usages of this group of drugs is in the treatment of hormone receptor-positive premenopausal breast cancer, where they are administered in conjunction with tamoxifen[60] or aromatase inhibitors[61], or for the preservation of ovarian function at the time of chemotherapy.[62,63]

Therefore, this category of compounds seems an alternative for the treatment of some menstrual disorders when breast cancer is the concern.

In conclusion, most non-oral hormonal methods of contraception and other available hormone compounds prescribed for the treatment of hormonal disorders are safe for temporary use, except for women with breast cancer, for whom analogues of gonadotropin-releasing hormone may be considered a safe hormonal prescription.

**Conflict of Interest**

None.

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