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Is ovulation induction with letrozole in breast cancer patients still safe even if it could increase progesterone levels?

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Abstract. – Very high progesterone levels (mean 186.6 ± 43.6 ng/mL) during the luteal phase were found in a small study of breast cancers patients undergoing controlled ovarian stimulation (COS) with letrozole plus recombinant FSH. Results highlight the need to further evaluate this in larger series. While waiting, the clinical significance of high progesterone levels can be drawn from epidemiological and experimental data here reviewed in order to give reassurance to the clinician involved in fertility preservation. If the progesterone increase will be confirmed, epidemiological and experimental data do not seem to indicate a detrimental effect or they could even be protective. As this possible rise of levels is a very short event in the very long lasting and multifactorial breast carcinogenesis, it is unlikely that it will significantly influence breast cancer prognosis.

Key Words:
Breast cancer, Fertility protection, Letrozole, Progesterone, Ovulation induction, Infertility.

Introduction

Around 10% of all breast cancers occur during reproductive age, and fertility preservation strategies are of utmost importance for this special population of young patients [1].

To effectively collect an adequate number of oocytes and to limit the rise of estradiol after gonadotrophins administration, a number of regimens, including the anti aromatase letrozole, have been developed. Recent results have confirmed the safety and feasibility of this approach[2,3]. Nonetheless, few data are available about the modulation of hormones, a part from estradiol, when young breast cancer patients are submitted to ovarian stimulation regimens including letrozole.

In the study by Alviggi et al[4], progesterone levels in the mid-luteal phase were evaluated in 3 patients undergoing controlled ovarian stimulation (COS) in the presence of the aromatase inhibitor letrozole plus recombinant FSH. Ovulation was induced with hCG in one case or with GnRH agonist in the other two. Patients continued letrozole treatment after oocyte collection. Very high progesterone levels (mean 186.6 ± 43.6 ng/mL) were found in all three cases during the luteal phase. These results, although preliminary and limited to only 3 cases, need consideration for the possible role of progesterone in the transformation of a sensitive stem cell population in the mammary glands[5]. In a previously published larger case control study by Goldrat et al[6], luteal phase progesterone levels did not differ significantly between 21 breast cancer patients who underwent controlled ovarian stimulation (COS) with aromatase inhibitors, and a control group of 21 infertile patients treated with standard GnRH-a COS ($p = 0.092$). There was only slight increase ($\leq$ 60 ng/ml) in progesterone levels in women treated with aromatase inhibitors. This study differs from that by Alviggi et al[4], as all women underwent triggering with hCG, and GnRH-antagonist was used during the luteal phase in only 10/21 women treated with letrozole.

Progesterone is frequently increased during COS, even without letrozole, as its level should exceed 80-100 nmol/L (approximately 25 ng/mL) during the luteal phase to obtain a higher reproductive outcome. hCG triggering of final oocyte maturation results in higher progesterone levels, usually exceeding 60 ng/ mL, than in triptorelin

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triggering, where levels exceed 50 ng/mL, on the day of transfer and one week later[7].

When progesterone plus hCG supplementation is prescribed in COS cycles with hCG triggering, the mean progesterone level is below 95 ng/ mL 6 days after oocyte retrieval[8]. So progesterone values (mean 186.6 ± 43.6 ng/ mL) as in the study under consideration[4] are, therefore, unexpectedly high.

Alviggi et al[4] speculated that "the estrogen negative feedback effect on the hypothalamus-pituitary axis and the disruption of steroid biosynthesis could represent an intriguing reason behind this phenomenon". Letrozole could reduce estradiol production during the luteal phase, thereby inhibiting the estrogen-negative feedback on the hypothalamus-pituitary axis. LH levels may rise above physiological values and stimulate progesterone synthesis. Alternatively, the disruption of the steroid biosynthesis pathway associated with letrozole-induced inhibition of aromatase could provoke upstream accumulation of steroid precursors including progesterone.

These data need further evaluation in larger studies. Even if the transient progesterone increase will be confirmed, the clinical relevance is still under debate as its role in the pathogenesis of breast cancer is still unclear[9,10].

Epidemiological data seem to confirm progesterone's involvement in breast cancer development, but using progestogens (like medroxy progesterone acetate), instead of natural progesterone, in menopausal hormonal therapy (MHT)[11]. No significant relative risk of breast cancer was found among patients who used natural progesterone 1.00 (CI 0.83-1.22, $p > 0.05$) in MHT[12].

Breast cancer risk doesn't seem significantly increased with newer hormonal contraceptives, also because intra mammary steroid production is favorably modified[13].

In the European Prospective Investigation into cancer and nutrition (EPIC)[14], the absolute risk of breast cancer for women younger than 40 followed up for 10 years was estimated at 2.6% for those in the highest quartile of serum testosterone *vs.* 1.5% for those in the lowest quartile, indicating that higher endogenous androgens are a risk factor. For the highest and lowest quartiles of progesterone, these estimates were 1.7% and 2.6%, respectively, suggesting that higher progesterone levels could be protective.

The very high progesterone levels during pregnancy seem also protective[15], even though the hormonal milieu in pregnancy is much more complex, precluding to extrapolate the net effect of progesterone.

Breast cancer risk is difficult to be evaluated, as it is multifactorial[16]. Environmental and genetic factors contribute to the complex and long lasting breast cancerogenesis[17,18]. Polymorphisms explain differences among individuals and ethnic groups, and may exhibit genetic heterogeneity with respect to steroid disposition and disease susceptibility; thus, epidemiological research is complex to extrapolate to other populations[19].

Some *in vitro* data on progesterone receptors are also reassuring as greater than 50% of estrogen receptor (ER)-positive breast cancers co-express the progesterone receptor (PR), which can directly and globally modify ER action to attenuate tumor growth[20].

Progesterone inhibited estrogen-mediated growth of ERα+ cell line xenografts and primary ERα+ breast tumor explants and had increased anti-proliferative effects when coupled with an ERα antagonist, with good clinical outcome[21]. Patients with ER positive invasive breast cancer with high PR expressing tumors have a better prognosis than those with low PR expressing tumors, and need less chemotherapy[22]. Progesterone receptor has two isoforms (PR-A and PR-B): a high PR-A/PR-B ratio is associated with poor prognosis[23].

Other experimental results need consideration, as progesterone induces adult mammary stem cell expansion[24]. This effect could be mediated by a paracrine mechanism through the receptor activator of nuclear factor kappa-B ligand (RANKL) paracrine signaling and may drive the dissemination of cells from microscopic breast tumors to distant metastatic sites very early in tumor progression[25].

The cancerogenic effects could mostly be related to the steroids directly produced by the breast than from those from the circulation. The intracrinology of breast cancer is better studied in menopause[26] and is hard to consider if ovulation induction can significantly affect it.

Progesterone can be converted into many other steroids that may bind its nuclear receptor or membrane receptors, as shown for the progesterone metabolite, 5α-pregnane-3,20-dione (5α-dihydroprogesterone; 5αP). The possible cancer-promoting effects of administered progesterone, could in fact be due to the locally produced progesterone metabolite, 5αP, and not due to progesterone itself, and could be inhibited by the

5α reductase inhibitor finasteride[27]. Other progesterone metabolites, like 4-pregnenes such as 3αHP, are associated with decreased cell proliferation and detachment[28]. Thus. the breast effects change according to the varying progesterone metabolism.

The increase of progesterone in the study by Alviggi et al [4] is of very short duration, compared with the lifetime effect of endogenous hormones or years of hormonal therapies. Breast carcinogenesis is a very long lasting event affected by genetic, epigenetic, and lifestyle factors, so a net effect on breast cancer prognosis of few days of progesterone increase is difficult to measure or unlikely to be significant [29,30].

Conclusions

Alviggi et al[4] results highlight the need to further evaluate in larger series progesterone levels in the luteal phase in women with breast cancer undergoing controlled ovarian stimulation (COS) with letrozole. If the progesterone increase will be confirmed, epidemiological and experimental data seem not to indicate a detrimental effect. As the progesterone increase with COS is a very short event, in the very long lasting multi factorial breast carcinogenesis, it is unlikely that it will negatively and significantly influence breast cancer prognosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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