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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

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