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Human chorionic gonadotropin as an angiogenic factor in breast cancer during pregnancy

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Summary Breast cancer associated with pregnancy is defined as the one in which the diagnosis is made in a pregnancy or within one year of delivery. Breast cancer is the second most common malignancy during pregnancy and it is generally considered to have a worse prognosis than the one that is not associated with pregnancy. The average patient is between 32 and 38 years of age. Steroid hormone receptor-positive cell populations comprise 80% of breast cancers, however, estrogen receptor levels in pregnancy-associated tumors are often low or absent. Extensive laboratory data suggest that angiogenesis plays an essential role in breast cancer development, invasion, and metastasis. One of the most powerful stimulatory factors, vascular endothelial growth factor (VEGF), functions in autocrine/paracrine pathways. Current research, generally has validated the poor prognosis and early relapse that are associated with increasing microvessel density, which is related to VEGF expression in tumoral cells. During pregnancy, human chorionic gonadotropin (hCG) induces neovascularization in various tissues, one of them being the placenta. Its receptors have been detected in epithelial cells in breast carcinoma tissue, and breast cancer cell lines. According to this premise the hCG normally produced during pregnancy could induce the synthesis of VEGF and by this means stimulate the development and metastatic potential of breast cancer cells in the pregnancy period.

Thus, research involving hCG and VEGF would help us understand the physiopathology of breast cancer during pregnancy, as well as provide us with probable prognostic tools.

Introduction

Breast cancer associated with pregnancy is defined as the one in which the diagnosis is made in a pregnancy or within one year of delivery [1]. Only 1% — 2% of breast cancer overall is diagnosed during pregnancy or lactation [2]. Nevertheless, it is the second most common cancer in pregnant women, after cervical cancer, occurring in about 1 in 3000 pregnant women [3]. The average patient is between 32 and 38 years of age [4]. Breast masses discovered during pregnancy should receive thorough evaluation. Delay in the diagnosis of breast cancer in pregnancy may cause increased mortality and should be

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avoided [5], this is a reason why pregnancy is considered a risk factor for breast cancer because the normal physiologic breast changes may mask a developing malignant mass [6]. This setback may contribute to the higher proportion of patients with advanced stage at presentation; late stage at diagnosis appears to be the only reason for the generally worse prognosis in these patients, as stage for stage, they have a similar course. It is thought that as women delay childbearing, the incidence of breast cancer during pregnancy may increase.

It is estimated that 10—39 women per 100,000 live births are diagnosed with breast cancer during pregnancy [7]. For premenopausal women one in three to four breast cancers is associated with pregnancy according to the precise definition [8]. Pregnancy and lactation are reported to decrease the overall risk of breast cancer in older women [9], however, for individuals younger than age 35 who are diagnosed with breast cancer, the association with pregnancy is related to a worse prognosis [10]. If there is some kind of mutation, mostly in *BRCA1* and *BRCA2* genes, the effect of pregnancy on breast cancer risk varies depending on the mutations present [11].

Reproductive factors are clearly important in the development of breast cancer, but their effect on the prognosis is uncertain. Women diagnosed with breast cancer in the two years after childbirth had 5 and 10 year survivals of 58.7% and 46.1%, respectively, compared with 78.4% and 66.0% for women whose last childbirth was more than two years before their diagnosis.

Treatment of breast cancer during pregnancy requires careful consideration of the risk of the disease and gestational age of the fetus, in conjunction with the patient's preferences. Chemotherapy should be deferred beyond the first trimester. Radiation therapy is contraindicated. Therapeutic abortion is not necessary, although women with high-risk disease may find this preferable.

The relationship between pregnancy and breast cancer is complex, and a lack of available data complicates decision-making for many women diagnosed with breast cancer during pregnancy or desiring to become pregnant after such a diagnosis [12].

There is no evidence that pregnancy in breast cancer survivors will decrease long-term survival; in fact, some studies suggest a potential protective effect of pregnancy after breast cancer in terms of the risk of recurrence. However, the available studies are limited by substantial potential biases.

Hormonal influence and tumorigenesis in breast cancer and pregnancy

Breast hypertrophy is related to hormonal changes and an increase in multiple hormones during pregnancy among which are estradiol, progesterone, estriol, cortisol, prolactin and insulin. All of them are involved in the augmentation of breast tissue and maturation of the ducts and lobules for lactation. The circulating progesterone levels increase by more than a 1000-fold, estrogens increase by 100-fold, corticosteroids by two to threefold and prolactin and insulin are increased significantly, compared to the non-pregnant concentrations [13].

Breast cancers are typically abundant in receptors for estrogen and progesterone, which are a sign of cellular differentiation and have a better prognosis than those without receptors. Early during breast cancer development there is a disruption of normal cell—cell communication and a switch to autocrine mechanisms of proliferation within the steroid hormone receptor-positive cell populations, which comprise 80% of breast cancers [14]. Estrogen-and progesterone-positive breast cancer cells are stimulated to proliferate in response to estrogens, and antiestrogen and aromatase inhibitor therapies are based on this property of steroid hormone-sensitive breast cancers.

The responsiveness of breast cancer cells to estrogens and progestins depends highly on the presence of additional growth factors and cytokines and the relative concentrations of steroid hormone receptors and their ligands. High (104 M) concentrations of progesterone induce apoptotic cell death and loss of *BRCA1* and cyclin A in breast cancer cells [15]. These effects may be especially relevant to pregnancy, during which estrogen and progesterone levels are higher relative to the non-pregnant state. Under these conditions, receptors are predicted to be saturated, functionally active, and rapidly turning over (i.e., apparent low abundance). Elimination of progesterone-positive breast epithelial cells via apoptosis under conditions of high circulating progesterone concentrations may explain partly the protection from breast cancer development conferred by early pregnancy and why termination of pregnancy does not significantly improve the outcome of established breast cancers.

Compared with breast cancers that are not associated with pregnancy, estrogen receptor levels in pregnancy-associated tumors are often low or absent. So by this means, the high levels of estrogen and progesterone during pregnancy do not play a

relevant role in the development and growth of breast cancer cells in this group of patients.

Several reports discussed that ER-positive and ER-negative (estrogen receptor = ER) tumors display remarkably different gene expression phenotypes [45]. Also, ER-negative tumor cells produced larger amounts of growth factors, such as VEGF, their receptors and cytokines that can stimulate various types of cells including endothelial cells [46].

Breast cancer and angiogenesis

Angiogenesis is crucial in tumor development and progression. Very little is known about the regulation of angiogenesis in the normal breast. Vascular endothelial growth factor (VEGF) has a key stimulatory role in angiogenesis. This factor functions in autocrine/paracrine pathways; therefore, direct measurements in the target tissue are needed. In breast tissue, VEGF levels increase in the luteal phase, compared with the follicular phase but plasma VEGF does not show a cyclic variation. This may be one mechanism by which sex steroids contribute to breast cancer development [16].

Extensive laboratory data suggest that angiogenesis plays an essential role in breast cancer development, invasion, and metastasis. Hypoxia is a key signal for the induction of angiogenesis through hypoxia-inducible factors (HIF-1 and HIF-2). These consist of α and β subunits. The β subunit is expressed constitutively, whereas the α subunit is protected from degradation under hypoxic conditions. HIF-1α expression is greater in poorly differentiated lesions and is associated with increased proliferation and expression of the estrogen receptor and vascular endothelial growth factor (VEGF). A study by Salven and his group reported that VEGF protein is expressed in women breast cancer, with both VEGF-B (preferentially expressed in endothelial cells) and VEGF-C (associated with development of lymphatic vessels) also being expressed at lower levels [17].

Clinicopathologic correlations also confirm the central role of angiogenesis in breast cancer progression. Fibrocystic lesions with the highest vascular density are associated with a greater risk of breast cancer. There are two distinct vascular patterns in association with ductile carcinoma in situ: a diffuse increase in stromal vascularity and a dense rim of microvessels that are adjacent to the basement membrane of individual ducts [18]. Microvessel density was greatest with histopathologically aggressive ductal carcinoma in situ (DCIS) lesions and was associated with increased VEGF expression [19,20].

In two studies made by Guidi and colleagues [20,21] a significant association was found between VEGF mRNA expression and the degree of angiogenesis in biopsies from ductal carcinoma in situ and also a strong tumor cell expression of VEGF in half of the ductal breast carcinomas in situ and strong or moderate VEGF expression in most of the invasive carcinomas examined; a strong intratumoral endothelial cell expression of VEGF receptors was also observed in the second study.

The treatment of metastatic breast cancer with antibodies against VEGF (bevacizumab) and chemotherapy has been studied and showed a better response rate but no improvement in survival. The inhibition of VEGF action represents a potential therapeutic target in malignant tumors, such as breast cancer, with either antibodies, such as bevacizumab or kinase inhibitors of VEGF like vatalanib which are currently being studied [22,23].

VEGF and breast cancer prognosis

The current studies, generally, though not uniformly, have validated the poor prognosis and early relapse that are associated with increasing microvessel density [24]. Increased VEGF expression was also associated with impaired response to tamoxifen or chemotherapy in patients who had advanced disease.

Gasparini made a review of multiple investigation protocols in which VEGF is studied as a prognostic factor in breast cancer according to overall or relapse-free survival and, specially in his study, node negative or positive stage; in most of them it is suggested that VEGF plays a relevant biological role in the progression of breast cancer by its angiogenic characteristics and concluded that intratumoral VEGF status is an independent prognostic indicator of primary breast cancer [25]. Therefore, VEGF is an important marker that promises to be a prognostic tool in breast cancer.

A study in women with primary breast cancer showed a significant inverse correlation between free or total VEGF and ER status; it was also found that low sVEGFR-1 levels, which is a soluble receptor for VEGF and an intrinsic negative counterpart of VEGF signaling, and high total VEGF were significantly associated with poor prognosis, disease-free survival and overall survival; the sVEGFR-1 was specially significant as a prognostic indicator in ER-negative tumors [26]. Being a potential prognostic marker during pregnancy.

During pregnancy VEGF serum concentrations rise continuously during the first trimester, even without the presence of the corpeus luteum, until they reach a plateau, these levels are significantly and positively correlated to hCG, which also rises considerably during the first trimester, and estrogen levels according to a study by Evans et al [27].

Human chorionic gonadotropin (hCG) physiologic role

Human chorionic gonadotropin (hCG) is a heterodimeric hormone primarily produced by the placenta; it is also produced by other normal and cancer tissues in small amounts [28]. Elevated β-hCG levels most commonly are associated with pregnancy, germ cell tumors, and gestational trophoblastic disease [29]. It belongs to the glycoprotein hormone as well as to the cystine knot growth factor families, which include follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), platelet-derived growth factor-β (PDGF-β), transforming growth factor β (TGF-β), and vascular endothelial growth factor (VEGF). It has been found that approximately 80% of the first 115 amino acids of the β subunit of hCG are homologous to those in the subunit of luteinizing hormone (LH). LH and hCG bind to the same transmembrane glycoprotein receptor that belongs to the G protein-coupled receptor superfamily, hCG binds with higher affinity than LH.

Maternal serum hCG levels exponentially increase and reach a peak by about the end of the first trimester, followed by a rapid decline to low steady-state levels of approximately one tenth of the peak values [30]. There is strong circumstantial evidence that GnRH, synthesized in both the cytotrophoblast and syncytiotrophoblast, may be an important factor in hCG secretion during pregnancy [31]. One of the major functions of hCG during pregnancy is the ''rescue'' of the corpus luteum during the conception cycle [32].

In a study by Wulff after hCG-induced luteal rescue there was a significant increase in endothelial cell content of the corpus luteum. This suggests that the rescue of the human corpus luteum is associated with an increased angiogenic activity; the molecular mechanisms are not fully elucidated but involve the expression of VEGF and angiopoietins, this is related to the increased levels of VEGF mRNA in the human corpus luteum after hCG treatment; also during the rescue with hCG there is a high pericyte coverage which is associated to vessel stabilization [33]. The gonadotropin LH/hCG hormones also play a fundamental physiological role in the control of steroid production and gametogenesis. The gonadal actions of LH/hCG result in increased synthesis of steroid hormones, which in turn interact with different targets. The nongonadal actions of these hormones are not fully defined and vary according to the target organs and their physiological conditions. The density of the receptor as expressed by different tissues represents the principal mechanism of hCG modulation [34].

Human chorionic gonadotropin (hCG) and angiogenesis

Neovascularization and angiogenesis are two processes required for normal placental development; when there is inadequate placental perfusion, the trophoblast responds typically by proliferation that manifests by increased hCG secretion [35].

It has been found that hCG has a role in the angiogenesis process *in vivo* and *in vitro* by increasing capillary formation and migration of endothelial cells directly related to the quantity of hCG administered independently of its origin (recombinant or tumor produced), the neovascularization induced by hCG was similar to that produced by VEGF and basic fibroblastic growth factor (bFGF) [36]. These data indicate a direct novel function for human chorionic gonadotropin (hCG), a hormonal factor of trophoblastic origin in uterine adaptation to early pregnancy as well as in tumor invasion and underline the importance of hCG as a yet unrecognized angiogenic factor [37].

During pregnancy the presence of hCG receptors on trophoblast cells [47] may enable hCG to initiate VEGF transcription in the placenta. Exposure of human granulosa cells to hCG stimulates the expression of VEGF mRNA [48], administration of hCG in women undergoing *in vitro* fertilization increases urinary VEGF concentrations [49] and serum and follicular fluid VEGF concentrations [50].

Hypothesis

In women, LH/hCG receptors were detected in epithelial cells in normal breast tissue, benign breast lesions, breast carcinoma tissue, and breast cancer cell lines [38,39]. In cultured women breast epithelial cells, LH/hCG signaling exerts an antiproliferative effect under some culture conditions, decreases the expression of estrogen receptors, and activates apoptotic gene expression [40,41].

Depending on the culture conditions, hCG exerts either a stimulatory or an inhibitory effect on the growth of female human breast cell lines. This hypothesis is supported by epidemiological studies indicating that early parity, late menarche and early menopause have protective effects against breast cancer. However, contradictory results were obtained by another group in a different mouse mammary adenocarcinoma model. Rao demonstrates that hCG has anti-proliferative and anti-invasive effects in MCF-7 cells by down-regulating NF-κB and AP-1. These findings support the premise that hCG could be responsible for the pregnancy-induced protection against breast cancer in women [42]. However, in cultured MCF-7 human breast cancer cells, hCG has also been reported to stimulate cell growth by promoting intracellular conversion of androgens to estrogens.

An extremely rare type of breast cancer called breast carcinoma with choriocarcinomatous features (BCCF) is a highly malignant tumor with poor prognosis [43]. The tumor cells show positive immunoreactivity to human chorionic gonadotropin (hCG), as well as an elevated serum hCG. Most patients die within a few months because of multiple metastases [44].

According to this information there is a possibility that the worse prognosis of breast cancer observed during pregnancy is related to the high levels of hCG and its probable induction of tumoral angiogenesis by the production of VEGF which in turn allows tumoral growth, development, and its invading and metastatic potential.

Clinical Implications

The verification of this hypothesis could generate a potential therapeutic target and prognostic marker for breast cancer during pregnancy. Investigation could be directed towards a more focused delineation of the relationship between VEGF and hCG in breast cancer and therefore the availability of information for decision taking.

Conclusions

Increased VEGF expression is associated with an overall worse prognosis in breast cancer. The hCG normally produced during pregnancy could induce the synthesis of VEGF and by this means stimulate the development and metastatic potential of breast cancer cells in the pregnancy period. On the other hand, diverse non-tumoral models have shown that hCG stimulates VEGF synthesis; research involving breast cancer, hCG and consequently VEGF during pregnancy and the growth in this area of investigation would hopefully help us understand the physiopathology of breast cancer during pregnancy.

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