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Pre-Eclampsia and Breast Cancer Risk: "Fertile" Ground for Elucidating New Mechanisms of Prevention?

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According to American Cancer Society statistics, more than 230,000 new cases of breast cancer were estimated to have been diagnosed in 2011, with nearly 40,000 deaths attributable to this most common malignancy among women [1]. Historically confirmed factors known to raise a woman's risk for breast cancer include: increased patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone replacement therapy, especially an estrogen-progestin combination; previous exposure to ionizing radiation to the chest wall; benign proliferative breast disease such as atypical ductal hyperplasia [2]; increased mammographic density; and genetic mutations of BRCA1 or 2 [3]. In epidemiologic studies, specific pregnancy-related factors associated with lowering the risk of breast cancer have included early age at first full-term pregnancy [4-7]; increased number of births or parity [4,8]; longer duration of breastfeeding [4,7,9,10]; as well as a history of pre-eclampsia [4,11-13]. In December 2011, the Institute of Medicine published and also presented at the San Antonio Breast Cancer Symposium a statement that of reproductive factors that may impact breast cancer risk, but further research is needed [14-15]. Interactions between genes and their environment must be considered, and is certainly a call for further elucidation of mechanisms which may not only serve as protective to females at risk for breast cancer but also many determine mechanisms for intervention for those at higher than average risk for breast cancer.

In a Mini-Symposium of the San Antonio Breast Cancer Symposium of 2011 [16], further discussion highlighting environment and breast cancer risk, primarily the hormonal environment to which a woman and her female offspring are exposed, also put into focus pre-eclampsia as one such risk factor. Pre-eclampsia is defined as a triad of edema, hypertension, and proteinuria occurring primarily in nulliparas and after the 20th gestational week of pregnancy [17]; this condition can lead to endothelial cell injury, altered vascular reactivity resulting in hypertension, reduced glomerular filtration, compromised placental perfusion, and can lead to central nervous system involvement with seizures in eclampsia. This may be an autoimmune phenomenon induced as fetal trophoblasts imbed *in utero*, as characterized by research on maternal autoantibodies [18], which then further impacts maternal hypothalamic/pituitary hormones and subsequently the adrenal axis, which are normally engaged in multiple aspects of crosstalk during pregnancy as impacted by the contributions of the placental tissue [19]. Despite the serious nature of this condition, which may impact both fetal and maternal morbidity and mortality, there have been a number of case series reported in the literature, however, which suggest that having pre-eclampsia during pregnancy may actually confer a decreased risk of breast cancer in the future. Chief among these epidemiologic studies is one of several by Terry et al. [20] of Columbia University, whose group compiled data from a large, population-based case-control study of breast cancer conducted between 1996–1997 on Long Island, New York, finding that preeclampsia was inversely associated with breast cancer (with an odds ratio of 0.7 and 95% confidence interval of 0.5 to 1.0); the reported association was found to be even stronger among women who had multiple occurrences of preeclampsia (with an odds ratio of 0.3 and 95% confidence interval of 0.1 to 0.9), more pronounced among postmenopausal women, but was unrelated to gestational length. Vatten et al. [21] reported a cohort study combining information both the Medical Birth and the Cancer Registries in Norway, and found that, as compared with other parous women, those with pre-eclampsia and/or hypertension diagnosed in their first pregnancy had 19% lower risk (with 95% confidence interval from 9 to 29%) for breast cancer, after adjustment for attained age, time of diagnosis, age at first birth, and parity, and was similar for both pre- and postmenopausal women.

A key review by Innes and Byers has explored several possible intracellular mechanisms from endogenous hormone generation in pre-eclampsia which may impact each other and thus breast cancer development [22]. These include reports of reduced estrogen levels in pre-eclamptic pregnancies as compared with uncomplicated pregnancies, concomitant with a deficiency in placental aromatization of the androgen precursors dehydroepiandrosterone (DHEA) and androstenedione to estrogen, and resultant buildup of these levels. Placental tissue itself from hypertensive pregnancies has shown decreased ability to aromatize these precursor androgens [23]. While the relation of androgens to the development of breast cancer is less clear in the literature than is the impact of estrogen, some epidemiologic studies have shown that androgen levels and breast cancer may be inversely related, especially in premenopausal women and those with a family history of breast cancer [24], and therefore further clarification is required. These androgenic alterations may even impact normal breast development. Forman [25] specifically reported that a cohort of offspring of preeclamptic pregnancies and of normotensive pregnancies followed from birth through 12.8 years showed lower estrogens levels in puberty compared to their normotensive offspring; high dehydroepiandosterone- sulfate levels (DHEAS) but low testosterone levels were found in girls aged 10 years, and by 13 years, daughters of pre-eclamptic pregnancies had a 20% lower risk of mature breast tissue development (with odds ratio of 0.80 and 95% confidence interval from

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0.7 to 1.00). This may serve as a springboard for understanding these influences and thus interplaying mechanisms.

Preeclampsia is also characterized by elevated levels of progesterone [17]. Tamimi et al. [26] have shown that in a cohort of 260 Caucasian women in Boston, Massachusetts, was followed through pregnancy, elevated levels of progesterone collected in maternal blood was at the 27th week of gestation were associated with the likely development of pre-eclampsia (relative risk ratio of 2.65, with 95% confidence interval of 1.46-4.81), and that levels of sex hormone-binding globulin were inversely related to pre-eclampsia (risk ratio of 0.61, with 95% confidence interval of 0.31-1.20). *In vitro*, exogenous progesterone has been shown to inhibit estrogen-induced growth in breast tissue [27] and inhibits estrogen-induced proliferation of breast cancer cell lines [28-30] indeed, multiple prospective studies have reported lowered breast cancer risk with higher levels of endogenous progesterones in parous women [31]. In addition, a consistent demonstration in the literature has been that of markedly higher levels of placental human chorionic gonadotropin (hCG) in preeclamptic women as compared to normotensive pregnancies, with experimental studies showing hCG inhibiting growth in human breast cancer cell lines [32,33] and as a potent differentiating agent in rodent models of breast cancer, hCG may protect the mammary gland from promotion of neoplastic changes [32,34]. Preeclampsia has also been associated with low maternal and fetal levels of insulin-like growth factor-1 (IGF-1) and elevated levels of insulin-like growth factor binding protein (IGFBP) [35-41]. Linking these, recent animal models have further suggested that hCG may exert a protective effect on mammary tissue through induction of IGFBPs and reduced IGF-1 [42]. Importantly, IGF-1 may also play a synergistic role with estrogen in the pathogenesis of breast cancer, and also may help stimulate aromatization of estrone to more biologically active estradiol in breast cancer cells [43]. Preeclampsia has also been associated with high levels of the pituitary-adrenal axis neuropeptide corticotrophin releasing hormone (CRH), in both the maternal and fetal circulation [44], resulting in high cortisol levels [45]; in turn, high concentrations of placental CRH and fetal cortisol may also contribute to lowered activities of both estrogens and IGF-1, providing feedback for these levels. How these hormones all interact for feedback is especially important to continue to understand for normal breast development as well as for inhibiting carcinogenesis. Could these reduced exposures to active estrogens and higher androgen compounds may indeed impact upon breast cancer risk in the future, particularly for estrogen-responsive breast cancers?

Bridges and colleagues [46] have done important work studying rat models of preeclampsia where blood flow to the rat's placenta is restricted with clips and rat serum is harvested for protein expression, finding two primary factors increased and released during placental ischemia: soluble *Fms*-like tyrosine kinase-1, a soluble version of vascular endothelial growth factor (VEGF) and soluble endoglin, a co-receptor for transforming growth factor beta (TGF-β) [47]. Serum from these rat models of preeclampsia have also been shown to inhibit growth of breast cancer cells *in vitro* independent of estrogen receptor status and via engagement of intracellular signal transduction pathways. Gingery have reported in the FASEB Journal [48], that when soluble endoglin is incubated with estrogen-responsive MCF-7 and with estrogen-unresponsive LCC9 cells *in vitro,* their proliferation rates were reduced. In examining a mechanism via the intracellular MAP kinase/PI3K/Akt pathway, they found that Phospho-Akt and phosph-Erk1/2 activation was reduced in the MCF-7 cells at various intervals post-treatment with soluble endoglin, and surmise that soluble endoglin may act by attenuating TGFβ signaling, thereby inhibiting proliferation of MCF-7 breast cancer cells through the Akt and Erk intracellular signaling pathways [48]. How these factors may be exploited despite this maternal condition may impact prevention and even further targeted treatment of breast cancer [49]. For example, although Pritchard et al. [50] have recently concluded from a study combining 5 years of adjuvant tamoxifen with 2 years of high dose somatostatin receptor blocker and growth hormone secretion inhibitor octreotide did not initially improve progression-free survival or overall survival compared with tamoxifen alone in early stage hormone-receptor-positive breast cancer, Ameri and colleagues [51] advocate that targeting the actions of growth hormone and IGF-1 as their implications in mammary development and hyperplasia may be important for breast cancer prevention. They also report that a different somatostatin receptor inhibitor – pasireotide -- can block the action of estradiol and progesterone via IGF-1 inhibition in the mammary gland, and may further impact mammary hyperplasia. These, with interplay among the other cross talking mechanisms reviewed here as they converge in intracellular and finally nuclear signaling cascades, may be further prime targets in seeking to reduce risk of breast hyperplasia and carcinogenesis.

Discussion of these mechanisms and surrogates may serve as a catalyst to generating hypotheses toward longitudinal studies of women who have had pre-eclampsia and toward elucidating the hormonal environment which may change enough to positively impact breast cancer development in the mother and even offspring in the future; elucidating these could spark hypotheses toward preventive clinical trials for those at high risk for breast cancer. Further studies should be designed to follow women diagnosed with pre-eclampsia to overall pre- and post-menopausal breast cancer risk, stratified by family history, and correlated with surrogate markers in the serum as well as umbilical cord blood and placental tissue. Research is active for biomarker assay development based on placental mRNA candidate discovery genes [52], and small nucleotide polymorphisms (SNPs) of hormones may provide variants which contend as further explanations raising the risk of the development or protection against carcinogenesis [11,53]. Study of epigenomics [16] in the maternal uterine environment as well as the placental contribution will lead to more extensive understanding of the gene-environment interaction in pre-eclampsia for the purposes of prediction of future breast cancer risk for both the mother and her female offspring.

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