

Short Communication

A Mechanistic Hypothesis to Explain the Timing Hypothesis

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Submitted: 25 October 2014

Accepted: 03 Decembr 2014

Published: 05 Decembr 2014

ISSN: 2333-7125

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Keywords

- Adrenal steroids
- Menopause
- Menopausal transition
- Hormone replacement therapy
- Timing hypothesis

Abstract

The timing hypothesis posits that exogenous estrogen plus progestin (E+P) hormone therapy (HT) is generally beneficial when initiated in proximity to the final menstrual period, but this benefit decreases and can lead to increased risk when initiated six to ten years later. This concept has been put forward to explain the discrepancies across randomized clinical trials assessing HT for prevention of cardiovascular disease. Similarly, while postmenopausal estrogen alone therapy (E) is associated with a slight decrease in breast cancer, this decrease is not found with E+P. The timing hypothesis, therefore, provides guidance for future clinical care of menopausal women but does not address the underlying physiologic basis or mechanistic difference in either the timing or the HT regimen. However, longitudinal epidemiological data collected from mid-aged women and experimental studies in nonhuman primates provide additional information that may permit the associations found in population-based studies to hypothesize a causal pathway. Using the Bradford-Hill criteria for evoking causality, it is possible to posit that the increased incidence in cardiovascular disease and breast cancer during the menopausal transition induced under the influence of endogenous cyclic estrogen and progesterone, which leads to increased adrenal steroid production, is recapitulated by imposing exogenous E+P following the return of the adrenal to a pre-transition status.

ABBREVIATIONS

E+P: Estrogen plus Progestogen; **HT:** Hormone replacement Therapy; **CVD:** Cardiovascular Disease; **BrCA:** Breast Cancer; **LMP:** Final Menstrual Period; **LH:** Luteinizing Hormone; **DHEAS:** Dehydroepiandrosterone Sulfate; **DHEA:** Dehydroepiandrosterone

INTRODUCTION AND BACKGROUND

The timing of intervention with estrogen plus progestogen (E+P) as a hormone replacement therapy (HT) for mid-aged women has been suggested to have associations with differences in risks for cardiovascular disease (CVD) and possibly breast cancer (BrCA) in the late but not early postmenopause. Several large population-based studies have observed this effect [1-3] and others have hypothesized this in what is now referred to as the timing hypothesis to explain time-dependent differences in protective effects of specific HT regimens [4]. This hypothesis posits that exogenous HT is beneficial when initiated in proximity to the final menstrual period, but this benefit is lost when initiated 6-10+ years later, has been put forward to explain the discrepancies across randomized clinical trials

assessing HT for prevention of cardiovascular disease. Meta-analyses confirm that, in general, a timing hypothesis is not only applicable to CVD but also justifiable for cognitive effects [5]. However, such justification lacks a physiological basis, causal pathway or endocrine mechanism. No biological explanation for this phenomenon has been put forward even though a broader review of the physiology of women's healthy aging may provide the necessary information to satisfy Bradford Hill's criteria for considering documented associations as sufficient for indicating a causal pathway [6].

In the absence of a plausible mechanism for the time-specific adverse effects of E+P in the postmenopause, doubts have been raised primarily among some clinicians who feel the necessity for conserving the widest possible range of HT regimens available to them. This resistance to embrace such a conclusion is understandable in the absence of a firm biological explanation for associating a specific intervention with increased risks. In this regard, it may be instructive to compare the increased risks for CVD and BrCA that are associated with E+P intervention in the late postmenopause to those same increased risks that are observed during the menopausal transition [7-9]. In that comparison, it

can be suggested that the increased risks of postmenopausal intervention with E+P are similar to those that occur in the five to six years prior to the final menstrual period (LMP).

In addition to that parallel, recent findings provide evidence for a mechanistic explanation for E+P to induce changes in adrenal function that are not induced by E replacement alone. Briefly, there are now data to indicate that receptors for luteinizing hormone (LH) exist in the adrenal cortex of a wide range of species including higher primates [10] and humans [11]. These receptors appear to be nonfunctional until there is a decline in gonadal function, an induction of functionality of the adrenal LH receptors and a persistent rise in circulating LH. When these three events occur simultaneously during the menopausal transition, most women (i.e., 85%) exhibit a shift in adrenal steroidogenesis and increased circulating androgens [12]. This induction of adrenal androgen production occurs during the time that cyclic endogenous E+P is continuing despite a subtle decline in ovarian function.

An induction of a change in adrenal function under the domination of cyclic endogenous E+P is directly associated with the decline or removal of the gonads as an inhibitory factor. Observations in the nonhuman primate animal model reveal that immunoreactive LH receptors are present even in young animals and can be stimulated by pharmacologic challenges of chorionic gonadotropin but are not normally functional until the ovary is suppressed or removed [13]. Following the LMP in women, all three of these essential conditions for induction in a shift in adrenal steroid production exist. However, the adrenal induction that occurs during the menopausal transition remains at a plateau at and following the LMP [14]. Thus, further induction is not possible at this time even if exogenous E+P is imposed. This is consistent with the observation that E+P imposition does not increase risks in women during the first six years post-LMP. However, after six years post-LMP, the adrenal returns to its pre-transition condition as indicated by lower circulating dehydroepiandrosterone sulfate (DHEAS) levels. Exogenous E+P as a HT choice at this time is then capable of re-inducing the shift in adrenal steroid production and the reiteration of the same risks observed during the menopausal transition occur again.

A shift in adrenal function occurs spontaneously but unevenly among women only during the menopausal transition [14]. This shift occurs during the time that follicle stimulating hormone (FSH) is rising, which is the primary indicator of a decline in ovarian function. Despite this rise in FSH in all women, an adrenal shift is detected in only in 85% of women and the degree of shift is quite variable between individual women [15]. Thus, it seems likely that these women represent the susceptible individuals and those with greater shifts have greater risks. This elevation in adrenal androgens plateaus at the time of menopause and then declines over the next few years as the ability of the ovary to produce cyclic E+P is completely extinguished and the adrenal shift in steroid production disappears. Thus, the combined triad of events: decreased ovarian function, increased circulating LH and the activation of adrenal LH receptors by cyclic E+P represent the essential factors that result in a shift away from ovarian domination to increased influence by adrenal steroids in which increases of circulating adrenal steroids occur in some women. These same three conditions return in the late postmenopause in susceptible women when the previous induction has passed

and exogenous E+P regimens are added as a HT choice. It seems more than coincidental that these three conditions are associated with the same adverse outcome as observed during the menopausal transition and might be considered as evidence of causality. While increased adrenal medullary activities could also contribute to CVD there is no evidence that E+P interventions have such an effect. Receptors for LH have not been found in the adrenal medulla [10] and no increase in medullary size was observed following E+P HT therapy in the nonhuman primate animal model [16]. There is at least one report that increased cortisol and decreased aldosterone may also be involved in a gender- and ovarian stage-related fashion in mid-aged women but these events have not been directly linked the increased adrenal androgen production associated with E+P to date.

If true, then the collective evidence would provide a plausible hypothesis to explain how E+P induces CVD and BrCA risks in a time-dependent manner, why the timing of this induction is constricted to a specific window of time and why not all women have the same degree of response. This possibility can be examined in terms of the criteria established to determine if strong associations can be considered evidence of causality.

Using the Bradford Hall criteria [6], we can examine the evidence for suggesting a causal pathway in the following manner.

Temporality

This quality is demonstrated by the “recovery” period following the menopausal transition when endogenous cyclic E+P that induced the increase in adrenal $\Delta 5$ steroids ends. At the LMP, this induction ends and the adrenal cortex slowly returns to its pre-MT state over the next five to six years unless it is supported by continued E+P stimulation. This spontaneous regression of the adrenal cortex in the untreated postmenopause is indicated by the disappearance of the gender difference in DHEAS production during the late postmenopause.

Consistency

To date, all large studies with similar designs have made the similar observation that E+P but not E alone increases the risk for CVD only in women six years post-LMP. It is the consistency in response to E+P, whether endogenous or exogenous that satisfies this criterion. Further, not all women have the same adrenal trajectory during the menopausal transition and the response to E+P in the late postmenopause is similarly unevenly distributed among individual women.

Strength of association

The induction of adrenal androgens during the MT is disparate between women. While some women show no increase in DHEAS, others show a 600 to 800 fold increase in androstenediol and dehydroepiandrosterone (DHEA). While baseline levels of DHEAS are also disparate between women, especially between women of different ethnicities, as a group their relative change in adrenal androgens is similar [12]. It appears that that the “strength of response” to endogenous E+P is intrinsic and we, therefore, expect and observe this in the postmenopause and in response to exogenous stimulation.

Exposure-response

Women who do not receive E+P or E alone do not have an

increased risk for CVD. The “triad” requirements are present in all women during the MT but only 85% experience a detectable rise in DHEAS. This observation predicts that not all women will respond to E+P negatively, but those that do respond may have a variable response in both adrenal induction and increased adverse effects.

Reversibility

A gradual post-LMP decrease in CVD incidence in untreated women is an example of the reversibility of E+P induction in terms of the disappearance in the shift in adrenal steroid production.

Biologic plausibility

Ovariectomized macaques treated with E+P increase the width of their adrenal cortex and increase circulating DHEAS [16] while similar animal treated with E alone had no change in adrenal cortex physiology. In addition, macaques chemically castrated respond to chorionic gonadotropin with an increase in DHEAS [8]. Finally, receptors for luteinizing hormone have been demonstrated in the adrenal cortex of the laboratory macaque.

Analogy

Well-documented adverse effects of higher circulating androgens on CVD are recognized in both men and women. Women with an increase in adrenal androgen production have more androgens and are, therefore, more likely to have male-like health CVD outcomes. The effect on BrCA is more complex but at least one report indicates higher tissue levels of androstenediol, a specific adrenal androgen, in tumor tissues.

Specificity

Only E+P given to postmenopausal women at least five years after the LMP experience this specific adverse effect. In addition, this adverse effect is not associated with E alone.

CONCLUSION

Regardless of the interpretation of this hypothesis, it would be difficult if not impossible to support or deny by direct experimental design. Far too many women, too much money and serious ethical concerns prevent another large, longitudinal population-based study. However, since many women will continue to be prescribed various E+P regimens, these women can be recruited prospectively during their menopausal transition to determine their susceptibility to developing increased adrenal androgen production and the relation of that induction to CVD and BrCA risks prior to menopause. These same women can then be studied again during early and late menopause with respect to the type of HT they receive. The results of this study should provide direct evidence for both the mechanisms involved in increased risks as well as the involvement of the adrenal cortex in contributing to these risks.

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Cite this article

Lasley BL, McConnell DS, Crawford SL, Gee NA, Gold EB (2015) A Mechanistic Hypothesis to Explain the Timing Hypothesis. J Transl Med Epidemiol 3(1): 1037.