Studies on Menstrual Cycle Evaluation, Vaccination and Women’s Health

Leslie Carol Botha, Health Educator, Broadcast Journalist
Internationally Recognized Expert on Women's Hormones and Behaviors

Section V
I am 18 and my friends and I got the shots. Why did I get an autoimmune disorder and they did not?

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Impact of stress, gender and menstrual cycle on immune system: possible role of nitric oxide.
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Stress is a factor found to be involved in the etiology of many diseases. Gender and menstrual cycle phases are other factors affecting the predisposition of individuals for certain diseases. Results from animal and human studies suggest that the distribution of immune system cells may change at different phases of the menstrual cycle. Acute mental stress in humans alters immune variables, too. The increase in the number of natural killer (NK) cells is the most consistent finding among the immune variables, though there are controversies for the other lymphocyte groups. Nitric oxide (NO) as an immune mediator has an unsettled role whether it causes the redistribution of the immune cells, or is an end product of lymphocyte activation. This study was planned to investigate the effect of mental stress on lymphocyte subtypes and the role of NO, for men and women at different phases of the cycle. For this purpose, healthy men (n = 10) and women (n = 10), during the follicular and luteal phases underwent Stroop colour-word interference and cold pressor tests. The immune system responses before and after the tests were determined by cell counts with the flowcytometer. Menstrual cycle phase was ascertained by plasma estrogen and progesterone measurements. Stress response was evaluated by blood pressure (BP) and heart rate (HR) measurements throughout the tests and plasma cortisol and urinary metanephrine and vanillylmandelic acid (VMA) measurements before and after the tests. Plasma and urinary NO determinations were performed before and after the test was completed. All the results were analysed with the appropriate statistical methods. The luteal phase differed from the other groups due to the presence of suppressed immune response to acute stress, including decreased CD4/CD8 ratio and NK cell percentage. On the other hand, acute stress caused a shift from cellular to humoral immunity in men. As indicated by these results, individual reaction towards stress is affected by gender and menstrual cycle phase. NO appears to be a possible effector molecule for these differences.


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Sex Differences in Stress Response Circuitry Activation Dependent on Female Hormonal Cycle
Understanding sex differences in stress regulation has important implications for understanding basic physiological differences in the male and female brain and their impact on vulnerability to sex differences in chronic medical disorders associated with stress response circuitry. In this functional magnetic resonance imaging study, we demonstrated that significant sex differences in brain activity in stress response circuitry were dependent on women's menstrual cycle phase. Twelve healthy Caucasian premenopausal women were compared to a group of healthy men from the same population, based on age, ethnicity, education, and right handedness. Subjects were scanned using negative valence/high arousal versus neutral visual stimuli that we demonstrated activated stress response circuitry [amygdala, hypothalamus, hippocampus, brainstem, orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and anterior cingulate gyrus (ACG)]. Women were scanned twice based on normal variation in menstrual cycle hormones [i.e., early follicular (EF) compared with late follicular–midcycle (LF/MC) menstrual phases]. Using SPM8b, there were few significant differences in blood oxygenation level-dependent (BOLD) signal changes in men compared to EF women, except ventromedial nucleus (VMN), lateral hypothalamic area (LHA), left amygdala, and ACG. In contrast, men exhibited significantly greater BOLD signal changes compared to LF/MC women on bilateral ACG and OFC, mPFC, LHA, VMN, hippocampus, and periaqueductal gray, with largest effect sizes in mPFC and OFC. Findings suggest that sex differences in stress response circuitry are hormonally regulated via the impact of subcortical brain activity on the cortical control of arousal, and demonstrate that females have been endowed with a natural hormonal capacity to regulate the stress response that differs from males.

http://www.jneurosci.org/cgi/content/abstract/30/2/431

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Influence of menstrual cycle on NK activity

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Natural killer (NK) cells* are CD3- CD56+ and/or CD16+ cytotoxic lymphocytes that mediate first-line defense against various types of target cells without prior immunization. To assess the effect of the menstrual cycle and gender on NK activity we evaluated 30 healthy women (mean age 28.1 years, range
In follicular and luteal phases, 29 postmenopausal women (mean age 58.8 years, range 42-72) and 48 healthy men (mean age 31.6 years, range 21-40). In a flow cytometric test of NK activity, peripheral blood mononuclear effector cells were mixed with K562 targets cells labeled with DiO (3,3′-dioctadecyloxacarbocyanine perchlorate) at effector:target cell ratios of 40, 20, 10 and 5:1. Dead cells were stained with propidium iodide and results were expressed as lytic units per 10(7) cells. In addition, progesterone levels were determined in the luteal phase of the menstrual cycle of healthy women by a chemiluminescence assay. Our results showed that (1) NK cytotoxicity was higher in the follicular than in the luteal phase of the menstrual cycle (P < 0.0001); (2) postmenopausal women and men showed NK activity similar to women in the follicular phase but higher than women in the luteal phase of the menstrual cycle (P < 0.05); and (3) there was no correlation between NK activity and levels of progesterone. The data suggest that progesterone does not influence NK activity directly and that other factors may explain the reduction of NK activity in the luteal phase of the menstrual cycle.

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*Natural killer cells (or NK cells) are a type of cytotoxic lymphocyte that constitutes a major component of the innate immune system. http://en.wikipedia.org/wiki/Natural_killer_cell

PubMed.gov
Testosterone levels and cognitive functioning in women with polycystic ovary syndrome and in healthy young women
Schattmann L, Sherwin BB.

We investigated the possible influence of testosterone (T) on cognitive functioning in women with polycystic ovary syndrome (PCOS), an endocrine disorder associated with elevated levels of free testosterone (free T). Performance on a battery of neuropsychological tests in 29 women with elevated free T levels due to PCOS was compared to the performance of 22 age- and education-matched, healthy control women with free T levels in the normal female range. Women with PCOS had significantly higher levels of free T (estimated by the free androgen index) and demonstrated significantly worse performance on tests of verbal fluency, verbal memory, manual dexterity, and visuospatial working memory than the healthy control women. No differences between the groups were found on tests of mental rotation, spatial visualization, spatial perception, or perceptual speed. These results suggest that, in women, elevations in free T may be associated with poorer performance on cognitive tasks that tend to show a female advantage.

Hair Loss
Causes
By Mayo Clinic staff

Due to hormonal changes, irritation or damage, some hair follicles have a shorter growth phase and produce thinner, shorter hair shafts. Your hair goes through a cycle of growth and rest. The course of each cycle varies by individual. But in general, the growth phase of scalp hair, known as anagen, typically lasts two to three years. During this time, your hair grows just less than 1/2 inch (1 centimeter) a month. The resting phase is called telogen. This phase typically lasts three to four months. At the end of the
resting phase, the hair strand falls out and a new one begins to grow in its place. Once a hair is shed, the growth stage begins again.

Most people normally shed 50 to 100 hairs a day. But with about 100,000 hairs in the scalp, this amount of hair loss shouldn't cause noticeable thinning of the scalp hair.

Gradual thinning is a normal part of aging. However, hair loss may lead to baldness when the rate of shedding exceeds the rate of regrowth, when new hair is thinner than the hair shed or when hair comes out in patches.

**Causes of specific types of hair loss**

- **Alopecia areata.** This is classified as an autoimmune disease, but the cause is unknown. People who develop alopecia areata are generally in good health. A few people may have other autoimmune disorders, including thyroid disease. Some scientists believe that some people are genetically predisposed to develop alopecia areata and that a trigger, such as a virus or something else in the environment, sets off the condition. A family history of alopecia areata makes you more likely to develop it. With alopecia areata, your hair generally grows back, but you may lose and regrow your hair a number of times.

- **Telogen effluvium.** This type of hair loss is usually due to a change in your normal hair cycle. It may occur when some type of shock to your system — emotional or physical — causes hair roots to be pushed prematurely into the resting state. The affected growing hairs from these hair roots fall out. In a month or two, the hair follicles become active again and new hair starts to grow. Telogen effluvium may follow emotional distress, such as a death in the family or a physiological stress, such as a high fever, sudden or excessive weight loss, extreme diets, nutritional deficiencies, surgery, or metabolic disturbances. Hair typically grows back once the condition that caused it corrects itself, but it usually take months.

**Other causes of hair loss**

- **Poor nutrition.** Having inadequate protein or iron in your diet or poor nourishment in other ways can cause you to experience hair loss. Fad diets, crash diets and certain illnesses, such as eating disorders, can cause poor nutrition.

- **Medications.** Certain drugs used to treat gout, arthritis, depression, heart problems and high blood pressure may cause hair loss in some people. Taking birth control pills also may result in hair loss for some women.

- **Disease.** Diabetes and lupus can cause hair loss.

- **Medical treatments.** Undergoing chemotherapy or radiation therapy may cause you to develop alopecia. Under these conditions, healthy, growing (anagen) hairs can be affected. After your treatment ends, your hair typically begins to regrow.

- **Hormonal changes.** Hormonal changes and imbalances can cause temporary hair loss. This could be due to pregnancy, childbirth, discontinuation of birth control pills, the onset of menopause, or an overactive or underactive thyroid gland. The hair loss may be delayed by three months following a hormonal change, and it'll take another three months for new hair to grow back. During pregnancy, it's normal to have thicker, more luxuriant hair. It's also common to lose more hair than normal about three months after delivery. If a hormonal imbalance is associated
with an overproduction of testosterone, there may be a thinning of hair over the crown of the scalp. Correcting hormonal imbalances may stop hair loss.

http://mayoclinic.com/health/hair-loss/DS00278/DSECTION=causes

Science Direct
Luteinizing hormone provides a causal mechanism for mercury associated disease
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Summary
Previous studies have demonstrated that the pituitary is a main target for inorganic mercury (I-Hg) deposition and accumulation within the brain. My recent study of the US population (1999–2006) has uncovered a significant, inverse relationship between chronic mercury exposure and levels of luteinizing hormone (LH). This association with LH signifies more than its presumed role as bioindicator for pituitary neurosecretion and function. LH is the only hormone with a rare and well characterized, high affinity binding site for mercury. On its catalytic beta subunit, LH has the structure to preferentially bind inorganic mercury almost irreversibly, and, by that manner, accumulate the neurotoxic element. Thus, it is likely that LH is an early and significant target of chronic mercury exposure. Moreover, due to the role of LH in immune-modulation and neurogenesis, I present LH as a central candidate to elucidate a causal mechanism for chronic mercury exposure and associated disease.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WN2-4XP3C11-2&_user=10&_coverDate=11%2F13%2F2009&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=088cbd4b1b6837e023db2ef62e4df6ba#cor1

Safe Minds
Brief Assessment of Aluminum Exposure and Endocrine Disruption
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6/21/09
The brain is a main target of aluminum exposure and effect [1] where it induces neurodegeneration [2-4]. At high levels, aluminum has been demonstrated to inhibit prenatal and postnatal neurodevelopment in humans and animals [5-11]. Aluminum has been shown to target and accumulate in the hippocampus, the primary area of the brain associated with memory formation[12-14]. Aluminum exposure in human populations has been associated with deficits in cognitive function [15]. Aluminum neurotoxicity in children manifests symptoms of verbal impairment and regression [16]. Although the relationship between aluminum exposure and associated disease such as Alzheimer’s disease [13, 17-23], amyotrophic lateral sclerosis [24], and Parkinson’s disease [24, 25] remains to be fully elucidated, the specific toxicology of aluminum exposure on the endocrine system has been firmly established [26-31]. Aluminum deposits in the pituitary, parathyroid, and adrenals [32] and has been demonstrated to interfere with parathyroid hormone secretion [33-36], insulin like growth factor and T3 levels[37], and the reproductive system [28, 29, 31, 38].

It is thought that inflammation resulting from aluminum exposure may induce learning and memory deficits [39]. Certainly, targeted effects on the endocrine system may affect immune-modulation and produce a pro-inflammatory cascade that responds to targeted aluminum deposition in the hippocampus with resultant neurotoxicity.

Aluminum-containing adjuvants are used in certain vaccines to promote an immune response. The vaccines that contain aluminum adjuvants are: DTP (diphtheria-tetanus-pertussis vaccine), DTaP (diphtheria-tetanus-acellular pertussis vaccine), and some but not all Hib (Haemophilus influenzae type b) conjugate vaccines, Pneumococcal conjugate vaccine, Hepatitis B vaccines, all combination DTaP, Tdap, Hib, or Hepatitis B vaccines, Hepatitis A vaccines, Human Papillomavirus vaccine, Anthrax vaccine and Rabies vaccine.

There is demonstrated variability in aluminum neurotoxicity across species and age groups [40]. Therefore, it is likely variability in disease response to aluminum exposure exists within the human population. This variability may be due to variable elimination rates (kidney function, GI function), dietary intake, genetic predisposition, and previous exposure levels. Vaccine injections with aluminum bypass the usual biological barriers to absorption and thus confer maximal dose exposure. This bolus of aluminum (each vaccine may contain up to 850 ug of aluminum) may target specific regions of the brain and endocrine system, and in concert with the expected immune reaction, instigate a cascade of events leading to inflammation, neurotoxicity, and disease. There is no known physiological role for aluminum within the body and therefore it can be considered as only a deleterious influence [1]. As background levels of environmental aluminum exposure rise over time throughout the world, additional sourced of aluminum exposure should be eliminated, especially in vulnerable populations such as pregnant mothers, infants, and the elderly.

http://www.safeminds.org/mercury/docs/Brief%20Assessment%20of%20Aluminum%20Exposure%20and%20Endocrine%20Disruption.pdf

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Heavy Metals and Fertility

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Heavy metals have been identified as factors affecting human fertility. This study was designed to investigate whether the urinary heavy metal excretion is associated with different factors of infertility. The urinary heavy metal excretion was determined in 501 infertile women after oral administration of the chelating agent 2,3-dimercaptopropane-1-sulfonic acid (DMPS). Furthermore, the influence of trace element and vitamin administration on metal excretion was investigated. Significant correlations were found between different heavy metals and clinical parameters (age, body mass index, nationality) as well as gynecological conditions (uterine fibroids, miscarriages, hormonal disorders). Diagnosis and reduction of an increased heavy metal body load improved the spontaneous conception chances of infertile women. The DMPS test was a useful and complementary diagnostic method. Adequate treatment provides successful alternatives to conventional hormonal therapy.

http://www.informaworld.com/smpp/content~content=a713851573&db=all


Hormone Allergy
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Background
Estrogen and progesterone have been associated in women with symptoms that include asthma, migraine, dermatitis and pain.

Objective
We suggest a connection between symptoms associated with hormone changes to a hormone antibody response.

Methods
For IgG, IgM and IgE antibodies to progesterone, blood samples were obtained from 288 healthy control subjects by a commercial lab in California. Blood from 270 patients in Texas with changes in symptoms associated with menstrual cycles was examined. For IgE antibodies to both progesterone and estrogen, blood samples were obtained from an additional 32 healthy control subjects who had no symptoms related to menses and from 98 patients with symptoms associated with menstrual cycles. The symptoms were asthma, migraines and joint pain.

Results
At 2 S.D. above the mean values of control subjects, a significant number of patients show high levels of IgG, IgM and IgE antibodies to progesterone and estrogen.

Conclusions
This paper describes evidence of antibodies to the hormones estrogen and progesterone. Progesterone, estrogen and their metabolites, after binding to human tissue proteins, such as albumin or globulin, may act as antigens and promote Type 2 helper cell development, thereby regulating antibody synthesis and allergy. This leads to the possibility of treating a wide variety of disorders by determining hormone allergy and initiating desensitization. Two obvious applications for determination and treatment of hormone allergies are pre-menstrual asthma and menstrual migraines.

http://onlineallergycenter.com/folder/research_abstracts/Hormone_Allergy_AJRI_3_10_06.pdf

Immunological Adjuvants and Vaccines
NATO Advanced Study Institute on Immunological Adjuvants and Vaccines, 1988 : Akra Sounion, Greece
Edited by Gregory Gregoriadis, Anthony C. Allison, George Poste

...it has now been revealed that it is the aluminum which is put into vaccines as an adjuvant which causes production of IgE...the antibody of allergy and anaphylactic shock.

Al(OH)3 differs from other adjuvants not only in the range of antigens with which it is effective, but also in the isotype profile of the antibodies which are produced, which could influence the degree of protection afforded by a vaccine (see chapter by Allison in this volume). This aspect has been studied in the mouse, where Al(OH)3 is much less effective than FCA in potentiating IgG2 (Warner et al, 1968; BoMford, 1980a), but much more so for IgE (Hamaoka et al, 1973). This latter property of stimulating anaphylactic antibody might seem to be a disadvantage in a vaccine adjuvant, except when IgE contributes to protective immunity as is the case for schistosomes.

In a study of vaccination against Schistosoma mansoni in the mouse Al(OH)3 but not FCA provided protection, and this was correlated with anti-schistosomal IgE antibody (Horowitz et al, 1982).

(Schistosomes are trematode worms that live in the bloodstream of human beings and animals. Three species (Schistosoma haematobium, S. mansoni and S. japonicum) http://www.inchem.org/documents/iarc/vol61/m61-1.html

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Histamine Metabolism During the Menstrual Cycle

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The urinary excretion of histamine and its metabolites methylhistamine (MeHi) and methylimidazoleacetic acid (MelmAA) was measured during the menstrual cycle in nine healthy women, one allergic woman and three non-pregnant women with anovulatory regular cycles. Simultaneous urinary analyses of luteinizing hormone (LH) and total estrogens were performed. The healthy women showed individual variations in the excretion of histamine, MeHi and MelmAA. This observation has been interpreted as an expression of minor individual differences in the catabolism of histamine. At midcycle an increase in the urinary excretion of histamine metabolites was sometimes evident and a statistically significant correlation could be established between MeHi and estrogen in urine. These results may support previous findings of histamine release by estrogens in uterine tissue but may also reflect an elevated histamine formation. The allergic woman excreted constantly increased amounts of histamine and its metabolites, especially when her allergic symptoms became aggravated pre-menstrually. She did not exhibit any change in MelmAA excretion at midcycle but the MeHi-excretion varied with the excretion of estrogens in the urine. The subjects with anovulatory menstrual cycles had low values of histamine and metabolites although within the normal variations.


Additional Studies on Menstrual Cycle Evaluation and Women’s Health

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Infection and Immunity
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Nasal and Vaginal Vaccinations Have Differential Effects on Antibody Responses in Vaginal and Cervical Secretions in Humans
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Sexually transmitted diseases are a major health problem worldwide, but there is still a lack of knowledge about how to induce an optimal immune response in the genital tract of humans. In this study we vaccinated 21 volunteers nasally or vaginally with the model mucosal antigen cholera toxin B subunit and determined the level of specific immunoglobulin A (IgA) and IgG antibodies in vaginal and cervical secretions as well as in serum. To assess the hormonal influence on the induction of antibody responses after vaginal vaccination, we administered the vaccine either independently of the stage in the menstrual cycle or on days 10 and 24 in the cycle in different groups of subjects. Vaginal and nasal vaccinations both resulted in significant IgA and IgG anti-cholera toxin B subunit responses in serum in the majority of the volunteers in the various vaccination groups. Only vaginal vaccination given on days 10 and 24 in the cycle induced strong specific antibody responses in the cervix with 58-fold IgA and 16-fold IgG increases. In contrast, modest responses were seen after nasal vaccination and in the other vaginally vaccinated group. Nasal vaccination was superior in inducing a specific IgA response in vaginal secretions, giving a 35-fold increase, while vaginal vaccination induced only a 5-fold IgA increase. We
conclude that a combination of nasal and vaginal vaccination might be the best vaccination strategy for inducing protective antibody responses in both cervical and vaginal secretions, provided that the vaginal vaccination is given on optimal time points in the cycle.

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Menstrual influence on surgical cure of breast cancer
Hrushesky WJ, Bluming AZ, Gruber SA, Sothern RB
Department of Medicine, Albany Medical College of Union University, New York.
Erratum in:

In a retrospective study of 44 premenopausal women who underwent resection of a primary breast cancer and were followed for 5 to 12 years, disease recurrence and metastasis were more frequent and more rapid in women who had been operated upon during the perimenstrual period (days 0-6 and 21-36 of the menstrual cycle). By multivariate analysis, the time of resection in relation to the menstrual cycle is an independent predictor of the likelihood of future metastatic disease. Patients who underwent resection during the perimenstrual period had a more than quadrupled risk of recurrence and death compared with women operated upon during days 7 to 20 of the menstrual cycle.

Timing of Breast Cancer Surgery, Menstrual Cycle & Prognosis

| Institution: | University of California, San Diego |
| Investigator(s): | Hillary Klonoff-Cohen, Ph.D. - Hungyi Shau, Ph.D. - Helena Chang, M.D., Ph.D. |
| Award Cycle: | 1998 (Cycle IV) |
| Grant #: | 4EB-5900 |
| Award: | $506,070 |

Research Priorities
Innovative Treatments>Gene therapy and other treatments: new frontiers

Initial Award Abstract (1998)
Surgery is the most common treatment for early breast cancer. There may be a particular time during the menstrual cycle when breast cancer surgery is less successful and results in decreased survival. A multi-disciplinary research team consisting of an epidemiologist, reproductive hormone specialist, basic immunologist, and three breast cancer surgeons will evaluate breast cancer patients’ hormonal status to determine whether breast cancer surgery during a particular time of the menstrual cycle known as the follicular phase (i.e., occurring between menstruation and ovulation) will increase the chance that the tumor will re-occur. This three-year study will follow 400 White, African-American, Hispanic, and Asian or Pacific Islander premenopausal women who will undergo surgery for breast cancer at four different hospitals (University of California San Diego, University of California Los Angeles, Los Angeles County-University of Southern California, and USC/Kenneth Norris) between July 1998 and June 2001. Patients with other cancers, or those with a hysterectomy, will not be included in the study. A pathologist will
classify the type of breast cancer and where it has spread. The medical and reproductive histories, as well as other important information will be obtained from a detailed telephone interview, medical records, and laboratory results. The phase of the menstrual cycle (i.e., early or late follicular or luteal) will be determined by measuring specific hormones in the urine (e.g., progesterone, estradiol, follicle stimulating hormone, and leutinizing hormone) on a daily basis, starting on the day of surgery, and continuing until the onset of the next menstrual cycle. Most factors that influence the long-term outcome of breast cancer are beyond the doctor's control. This study will work with the body's predictable biologic rhythms (referred to as chronotherapy), in order to search for a better way to treat breast cancer. If the timing of surgical treatment during a particular phase of the menstrual cycle plays a significant role in survival from premenopausal breast cancer, this could possibly extend and/or save a great number of women's lives. In fact, the greatest benefit for timing of surgery would be to those young women at highest risk of breast cancer recurrence. The ease of modifying the timing of breast cancer surgery in the clinical setting could be very rapid and inexpensive; hence, timing of surgery could serve as a potentially simple, but powerful therapeutic tool.

In 2003, there were 211,300 new cases of invasive breast cancer and an estimated 55,700 addition cases of in situ breast cancer. The purpose of this study was to examine whether breast cancer surgery (i.e., lumpectomy, simple mastectomy, modified radical mastectomy) conducted during a particular phase of the menstrual cycle (i.e., early or late luteal or follicular) had an impact on long-term outcomes (i.e., recurrence, remaining healthy or death) among different racial groups. Scheduling breast cancer surgery around the menstrual cycle may have greater efficacy and result in fewer side effects than conventional therapies.

The preliminary analysis presented here is based on a sub-sample (n=200) of White, African American, Hispanic and Asian/Pacific Islander women who underwent surgery for primary carcinoma of the breast between 1998-2003, at UCLA Revlon Breast Cancer Center, Los Angeles County-University of Southern California, and Kenneth Norris Hospital. All women were interviewed by telephone 24 hours before surgery to obtain demographic, reproductive, medical, psychosocial, nutritional, occupational, and environmental information. In addition urine was collected daily, beginning 24 hours before surgery, and extending until the onset of the next menstrual cycle, in order to pinpoint the exact hormonal profile of the menstrual cycle. On average, the women were 40 years of age (range: 28-51 years) at the time of surgery, and were representative of all racial/ethnic groups in Southern California: Caucasian, 50.0%; Hispanic, 27.2%; Asian, 9.1%; Pacific Islander, 2.3%; African American, 2.3%; and Other/Mixed, 9.1%. Approximately 50% of women received their bachelor's degrees, while a further 21% had a total of 17-25 years of education. The mean number of years of education was 14 years (2-25 years) and ninety-one percent of women were employed at the time of diagnosis. Forty-three percent of women reported smoking (>100 cigarettes) during their lifetime, and 41% were exposed to second-hand smoke from their parents, spouses, or other adults. The majority of women (84%) reported consuming alcohol on a social or regular basis (>1 drink/week). The average age at menarche was 12.95 years (range: 10-15 years), and all women reported having regular menses. A total of 68% of women reported using oral contraceptives in their lifetime. Only 48% of the women ever breastfed. The overall distribution for stage of disease at diagnosis consisted of Stage 1 (21%), Stage 2 (45%), Stage 3 (5%), Stage 4 (3%), and unknown (24%). Fifty-three percent of women had ER positive tumors. Treatment options consisted of the following: 57% of women underwent breast conservation therapy, 30% had a mastectomy, 2.3% had surgery, NOS, 2.3% had a combination, and 9.1% were unknown. The overall recurrence rate was 20.5% for the
sample. When menstrual phase was divided as day 1-14 for the follicular phase and day 15 to the end of cycle as the luteal phase (based on self-report of the last 3 menstrual cycles), there was no statistically significant difference between the healthy and recurrent groups. However, when the menstrual phase was pinpointed according to the urine hormone measures, there was a statistically significant difference between the two groups of women (OR=2.12, p=0.04). Hence, women who were operated on in the follicular phase had a worse outcome (i.e., recurrence or death) than women in their luteal phase, while adjusting for stage of breast cancer, type of surgery, family history, and age. Estrogen receptor status, family history of breast cancer, and oral contraceptive use did not appear to substantially change the association. If these findings are replicated with the total sample, and subsequently in randomized clinical trials, this translational research (i.e., timing breast cancer surgery around the woman’s menstrual cycle), could be fairly easily implemented into the clinical arena as a simple, but powerful therapeutic tool, that could potentially extend and/or save a substantial number of women’s lives.

http://www.cbcrp.org/RESEARCH/PageGrant.asp?grant_id=241

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The Influence of Menstrual Cycle Phase on Surgical Treatment of Primary Breast Cancer: Have We Made Any Progress Over the Past 13 Years?
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The article by Love et al. (12) in this issue of the Journal adds fuel to this fire. In their article (12), the authors describe the results of a retrospective, unplanned analysis to determine whether the timing of surgery during the menstrual cycle influences outcome. One of the strengths of their work is that the analysis is based on a prospective randomized trial and, therefore, the treatments administered were prospectively determined and controlled. In addition, estrogen receptor assays were performed on the tumors of many of the patients, which helped to identify the group of patients most likely to be affected by this hypothesis. The results are of interest because, on the one hand, they appear to refute the hypothesis proposed by Hrushesky et al. (4) 13 years ago. According to Love et al. (12), in premenopausal patients treated with mastectomy or lumpectomy, the timing of surgery in relation to the phases of the menstrual cycle had no effect on outcome. On the other hand, Love et al. (12) report a secondary, unexpected result of their analysis: that the timing of ovarian ablation and initiation of tamoxifen therapy in relation to the phase of the menstrual cycle appeared to have a substantial effect on outcome. Premenopausal patients who had their breast surgery and ovarian ablation during the luteal phase of the menstrual cycle had a better disease-free and overall survival rate than premenopausal patients who had their breast surgery and ovarian ablation during the proliferative phase of the menstrual cycle.
Journal of Reproductive Immunology  
Volume 44, Issue 1, Pages 1-27 (September 1999)

Menstruation: induction by matrix metalloproteinases and inflammatory cells  
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Abstract

Menstruation occurs at the end of a normal reproductive cycle in the human female, following the fall in progesterone resulting from the demise of the corpus luteum. Current data support a central role for the matrix metalloproteinases in menstruation but their focal pattern of expression within peri-menstrual and menstrual endometrium suggests local rather than hormonal regulation. This review emphasizes the similarities between menstruation and an inflammatory process and examines the relationship between cells of hemopoietic lineage, particularly mast cells, eosinophils, neutrophils and macrophages, and the local production and activation of matrix metalloproteinases within the endometrium. It proposes a complex of critical regulatory circuits, initially activated by the withdrawal of progesterone, which provide interactions between the migratory cells that produce a myriad of important regulatory molecules and endometrial stromal and epithelial cells which produce both chemokines and matrix metalloproteinases. These mechanisms could account for the focal nature of the tissue degradation at menstruation.

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