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Relationships between Immune Function and Menstrual Cycle Stage

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Form B

IRB# _____

Date Received in Office of Research _____

THE UNIVERSITY OF TENNESSEE, KNOXVILLE

Application for Review of Research Involving Human Subjects

I. IDENTIFICATION OF PROJECT

Principle Investigators: Emma L. Taylor, Senior Nursing Student
University of Tennessee
College of Nursing
1203 Sutters Mill Lane
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Rachel M. Hodges, Senior Nursing Student
University of Tennessee
College of Nursing
2722 Scarlett Oak Court
Knoxville, TN 37909
(865)806-3010
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Faculty Advisor: Dr. Maureen Groer, PhD
University of Tennessee
College of Nursing

Project Classification: University Honors Senior Thesis

Project Title: Relationships between Immune Function and Menstrual Cycle Stage

Starting Date: Upon IRB Approval

Estimated Completion Date: March 31, 2005

External Funding: None

II. PROJECT OBJECTIVES:

The goal of this study is to analyze the relationship between immune function, infectious illness symptoms, premenstrual distress, and menstrual cycle stage in college-aged non-pregnant females. The menstrual cycle is divided into three phases: follicular, ovulatory, and luteal. Prior research also indicates changes in immune function during the phases of the cycle. During the ovulatory phase, IL-6, IL-8, and IL-1beta are differentially regulated (Al-Harhi et al., 2000). According to Agarwal and Marshall, the

type-1/type-2 cytokine balance is also affected near the time of menstruation as evidenced by a shift toward type-2 cytokines (1999). In a study of disease processes during the phases of the menstrual cycle, Lee, Bazar, and Yun postulated that the shift in immunity that they found involving Th-1 and Th-2 is due to autonomic balance (2004). One study found a direct relationship between the secretion of estradiol and the secretion of IgA by the parotid gland (Gomez et al., 1993). Groer et al (1993) found a relationship between menstrual cycle stage, menstrual cycle distress, and symptoms of infection in college-aged women. Studies have also shown a relationship between premenstrual syndrome (PMS) and hormone function that may affect immunity. Odber, Cawood, and Bancroft found that, unlike major depression where the underlying neurological changes are manifested as overactivity of the HPA axis, premenstrual depressive changes are associated with reduced HPA activity. Premenstrual depression may, therefore, be similar neurologically to seasonal affective disorder, which is associated with underactivity of the HPA axis (1998). Women with PMS in a study by Cornwell had "significantly higher mean levels of plasma cortisol" and differences in estradiol (2000). These findings support our study of cycle phase, premenstrual distress, and immune and infection variables.

III. DESCRIPTION AND SOURCE OF RESEARCH PARTICIPANTS:

The proposed study involves the formation of a voluntary sample based upon the following criteria: women aged between eighteen and thirty-five, weighing 110 pounds or more, non-pregnant, regularly menstruating with a 27-31 day cycle, able to speak and understand English, and willing and able to donate a blood sample of approximately 10 milliliters by venipuncture one time. Data collection will be between 8 and 9 am.

The participants will be informed of the study by flyers distributed to various UT campus organizations and UT campus bulletin boards. Estimated sample size is 100 women, evenly distributed across the three menstrual cycle stages with at least 30 participants per stage. Stage will be determined by date of last menstrual period. If the distribution of subjects by stage becomes skewed, volunteers will be asked to return for testing during a specific menstrual cycle stage.

IV. METHODS AND PROCEDURES

The blood will be analyzed for the following: ex vivo cytokine production, lymphocyte proliferation, serum levels of IL10 and Interferon-gamma, prolactin, cortisol, and ACTH. The statistical analysis will consist of correlations and regressions analyzing the relationships between distress and immune variables, and ANOVAs analyzing relationships between stage and immune variables.

V. SPECIFIC RISKS AND PROTECTION MEASURES

The foreseeable physical risks involved in this project are those normally involved with venipuncture, including pain, nausea, syncope, bruising. The foreseeable psychological risks include fear of venipuncture. Approval from The University of Tennessee's IRB will be sought and obtained before any subject is questioned or samples of blood are collected. Because the proposed study will involve human subjects, the researchers will take all possible precautions to ensure their protection. Racial and ethnic groups will be treated equally; all subjects will receive the same explanation of the

research purpose and procedures, the same consent form, and have access to the same support throughout the research period. Participants will be fully informed of their rights as participants and of the procedures involved in the research. Written consent to participate will be obtained from all participants.

Only after participants have received written and oral explanations of the study, any questions about the study have been answered, and written consent to participate in the study has been obtained will any questionnaires be administered or blood samples be drawn. Each participant will be assigned a number which will be used to identify their data and will be in no way tied to their actual identity. Completed surveys will be kept in a locked file cabinet in Room 345 of the College of Nursing.

VI. BENEFITS

There is the benefit to subjects of receiving information regarding their current immune function. Any values outside the range of normal will be reported to subjects for follow-up with their health care provider. This will be done by posting results by ID number on Dr. Groer's website. There is a benefit to science of determining any relationships between menstrual cycle, PMS, and immunity and infection.

VII. METHODS FOR OBTAINING "INFORMED CONSENT" FROM PARTICIPANTS

The study will be described orally and in writing to those who volunteer to participate in the study before they will be asked to sign the informed consent document. The research will be described as a study created to compare the relationship between immune function, menstrual cycle, and premenstrual syndrome. All description and explanation of the research will be provided in simple language and potential participants will have ample opportunity to ask questions of the investigators. The consent document will contain all basic elements of informed consent and a copy will be provided for the participants' use and information.

VIII. QUALIFICATIONS OF THE INVESTIGATORS

Emma Taylor and Rachel Hodges are undergraduate senior nursing student and the College of Nursing at the University of Tennessee. Both have completed the National Institute of Health (NIH) training module for the protection of human subjects. Both primary investigators have been trained in venipuncture procedures.

Maureen Groer has a PhD in physiology and biophysics and is a professor of Nursing. She manages the Kenneth Walker Nursing Science laboratory. She is competent in human subjects research and laboratory methodology.

IX. FACILITIES AND EQUIPMENT TO BE USED IN THE RESEARCH

Recruitment will take place by flyers posted around the University of Tennessee campus. The Kenneth Walker Nursing Science lab will be the site for much of the data analysis. The equipment in this lab is standard laboratory equipment for preparing serum samples and cell cultures.

X. RESPONSIBILITY OF THE PRINCIPAL INVESTIGATORS

Informed Consent Statement

Relationship between Immune Function and Menstrual Cycle Stage

INTRODUCTION

You are invited to participate in a research study designed to analyze relationships between immunity, menstruation, and premenstrual syndrome.

INFORMATION ABOUT PARTICIPANTS' INVOLVEMENT IN THE STUDY

As a subject of our study, you will answer a questionnaire for demographic information and another on premenstrual symptoms you had before your last menstrual period. You will then have blood drawn in the lab, which will be analyzed for immune markers.

The questionnaires will take approximately thirty minutes to complete, and the blood draw will take approximately fifteen minutes. We will be collecting blood samples during early to mid-January 2005.

RISKS

The possible foreseeable risks to you in this study include fear of having blood drawn, reliving painful memories brought up by the PMS questionnaire, mild pain during blood collection, bruising, nausea, fainting, and rarely hematoma (a bruise under the skin).

BENEFITS

There is the benefit to you of receiving information regarding your current immune function. You will potentially benefit from receiving information about significant findings of the study. There is a benefit to science of determining any relationships between menstrual cycle, PMS, and the immune system if any are found.

CONFIDENTIALITY

The information in the study records will be kept confidential. Data will be stored securely and will be made available only to persons conducting the study unless participants specifically give permission in writing to do otherwise. No reference will be made in oral or written reports which could link participants to the study.

Participant's initials _____

EMERGENCY MEDICAL TREATMENT

The University of Tennessee does not “automatically” reimburse participants for medical claims. If physical injury is suffered in the course of research, please notify the investigators:

Emma Taylor
Etaylor5@utk.edu

Rachel M. Hodges
rmorris6@utk.edu

Dr. Maureen Groer
(865)974-7615
mgroer@utk.edu

CONTACT INFORMATION

If you have questions at any time about the study or the procedures (or experience adverse effects), you may contact the researchers, Emma Taylor or Rachel M. Hodges at etaylor5@utk.edu or rmorris6@utk.edu respectively. If you have questions about your rights as a participant, contact the Compliance Section of the Office of Research at (865)974-3466.

PARTICIPATION

Your participation in this study is voluntary, and you may decline to participate without penalty. If you decide to participate, you may withdraw from the study at anytime without penalty and without loss of benefits to which you are otherwise entitled. If you withdraw from the study before data collection is completed your data will be returned to you or destroyed.

CONSENT

I have read the above information. I have received a copy of this form. I agree to participate in this study.

Participant's Signature _____

Date _____

Investigator's Signature _____

Date _____

Rachel M. Hodges and Emma Taylor (Maureen Groer, advisor)
Relationships between Immunity, Infection, and Menstrual Cycle Stage
Abstract

This research study is designed to analyze relationships between immunity, stages of the menstrual cycle, and premenstrual syndrome in college-aged, non-pregnant females. Previous studies have suggested a link between the immune system and the menstrual cycle. A better understanding of this relationship may aid in interpretation of the reproductive cycle and conception. The study was approved by the UT IRB. The participants, who were informed of the study by flyers, completed questionnaires for demographic information and premenstrual symptoms, and a blood sample was drawn in the lab. The analysis will compare cellular and humoral immune marker levels, menstrual cycle stage, and subjective responses to the premenstrual distress questionnaire and examine relationships among the variables.



Have you ever wondered what your immune system is doing during your menstrual cycle?

If you have, then come participate in our research study. We will draw a sample of your blood and test for specific immune cells in it. To participate in the study you need to be female who weighs at least 110 lbs and is between the ages of eighteen and thirty-five. If you are interested please contact any of the following:

***Rachel M. Hodges
Rmorris6@utk.edu***

***Emma Taylor
etaylor5@utk.edu***

***Dr. Maureen Groer
345 College of Nursing
Knoxville, TN 37996
(865)974-7615
mgroer@utk.edu***

DATE: _____

ID# _____

LAST MENSTRUAL PERIOD MODULE

1. On what date did your last period begin? ___/___/___
2. How long was your most recent full menstrual cycle (starting from the first day of your period to the day before you started your next period; average 24-35 days)? # DAYS: _____

Did these feelings cease by the end of your period or shortly thereafter? (check YES or NO)

How much did you experience each of these symptoms during the week BEFORE your last period?

	Not at all (1)	Minimal (2)	Mild (3)	Moderate (4)	Severe (5)	Extreme (6)	YES	NO
1. Did you feel depressed, sad, down or blue?								
2. Did you feel hopeless?								
3. Did you feel worthless or guilty?								
4. Did you feel anxious, tense, keyed up or on edge?								
5. Did you have mood swings, such as feeling suddenly sad or tearful?								
6. Were you more sensitive to rejection; were your feelings easily hurt?								
7. Did you feel angry or irritable?								
8. Did you have conflicts or problems with people?								
9. Did you have less interest in usual activities (i.e. work, school, friends, hobbies)?								
10. Did you have difficulty concentrating?								
11. Did you feel lethargic, tired, fatigued or have lack of energy?								
12. Did you have increased appetite or overeat?								

Relationships between Immune Function and Menstrual Cycle Stage

Introduction

You are invited to participate in a research study looking for relationships between the immune function and menstrual cycles and premenstrual symptoms of nonpregnant women.

Information about Participants' Involvement in the Study

As a subject of our study, you will answer a questionnaire for demographic information and another on premenstrual symptoms you had before your last menstrual period. You will then have blood drawn in the lab, which will be analyzed for immune markers.

The questionnaires will take approximately thirty minutes to complete, and the blood draw will take approximately fifteen minutes. We will be collecting blood samples during early to mid-January 2005.

Risks

The possible foreseeable risks to you in this study include fear of having blood drawn, reliving painful memories brought up by the PMS questionnaire, mild pain during blood collection, bruising, nausea, fainting, and rarely hematoma (a bruise under the skin).

Benefits

There is the benefit to you of receiving information regarding your current immune function. You will potentially benefit from receiving information about significant findings of the study. There is a benefit to science of determining any relationships between menstrual cycle, PMS, and the immune system if any are found.

Confidentiality

The information in the study records will be kept confidential. Data will be stored securely and will be made available only to persons conducting the study unless participants specifically give permission in writing to do otherwise. No reference will be made in oral or written reports which could link participants to the study.

Contact

If you have questions at any time about the study or the procedures, you may contact the researchers, Emma Taylor or Rachel M. Hodges at etaylor5@utk.edu or rmorris6@utk.edu respectively. If you have questions about your rights as a participant, contact the Compliance Section of the Office of Research at (865)974-3466.

Participation

Your participation in this study is voluntary, and you may decline to participate without penalty. If you decide to participate, you may withdraw from the study at anytime without penalty and without loss of benefits to which you are otherwise entitled. If you withdraw from the study before data collection is completed your data will be returned to you or destroyed.

Lit Review

The menstrual cycle is divided into three phases: follicular, ovulatory, and luteal. Prior research also indicates changes in immune function during the phases of the cycle. During the ovulatory phase, IL-6, IL-8, and IL-1beta are differentially regulated (Al-Harhi et al., 2000). According to Agarwal and Marshall, the type-1/type-2 cytokine balance is also affected near the time of menstruation as evidenced by a shift toward type-2 cytokines (1999). In a study of disease processes during the phases of the menstrual cycle, Lee, Bazar, and Yun postulated that the shift in immunity that they found involving Th-1 and Th-2 is due to autonomic balance (2004). One study found a direct relationship between the secretion of estradiol and the secretion of IgA by the parotid gland (Gomez et al., 1993).

Studies have also shown a relationship between premenstrual syndrome (PMS) and hormone function that may affect immunity. Odber, Cawood, and Bancroft found that

unlike major depression where the underlying neurological changes are manifest[ed] as overactivity of the HPA axis, premenstrual depressive changes are associated with reduced HPA axis activity. Premenstrual depression may, therefore, be similar neurologically to seasonal affective disorder, which is associated with underactivity of the HPA axis (1998).

Women with PMS in a study by Cornwell had “significantly higher mean levels of plasma cortisol” and differences in estradiol (2000). We think these findings are significant in the study of correlations between PMS and immune function.

Agarwal, S.K., and Marshall, G.D. Jr. (1999, September) Perimenstrual alterations in type-1/type-2 cytokine balance of normal women. *Annals of Allergy, Asthma, and Immunology*, 83(3), 222-8.

Al-Harhi, L., Wright, D.J., Anderson, D., Cohen, M., Matity, A.D., Cohn, J., Cu-Unvin, S., Burns, D., Reichelderfer, P., Lewis, S., Beckner, S., Kavacs, A., Landay, A. (2000, August) The impact of the ovulatory cycle on cytokine production: evaluation of systemic, cervicovaginal, and salivary compartments. *Journal of Interferon and Cytokine Research*, 20(8), 719-24.

Cornwell, J. (2000, April) Psychoneuroimmune relationships across the menstrual cycle and perimenstrual symptomatology. *Dissertation-Abstracts-International:-Section-B:-The-Sciences-and-Engineering*, 60, 4954.

Gomez, E., Ortiz, V., Saint-Martin, B., Boeck, L., Diaz-Sanchez, V., Bourges, H. (1993, May) Hormonal regulation of the secretory IgA (sIgA) system: estradiol- and progesterone-induced changes in sIgA in parotid saliva along the menstrual cycle. *American Journal of Reproductive Immunology*, 29(4), 219-23.

Lee, P.Y., Bazar, K.A., and Yun, A.J. (2004) Menstrual variation of autonomic balance may be a factor in exacerbations of certain diseases during the menstrual cycle. *Medical Hypotheses*, 63(1), 163-7.

Odber, J., Cawood, E.H., Bandcroft, J. (1998, December) Salivary cortisol in women with and without perimenstrual mood changes. *Journal of Psychosomatic Research*, 45(6), 557-68.

Participation

Under the supervision of Dr. Groer, we prepared the attached documents to seek IRB approval for the research study. After gaining IRB approval, flyers were hung on campus to recruit subjects. Once testing began, we were present in the lab for four weeks from Monday through Thursday, 3 pm until 7 pm, and Friday afternoon for approximately two hours. We instructed participants to respond to the questionnaires, then answered any questions they had concerning the study. We drew their blood, prepared it, incubated it, and froze it in order to do the assays at a later date. However, the plate reader in the Kenneth Walker Nursing Science laboratory has been sent off for repair and we are currently unable to obtain results. We plan on participating in the research further after graduation.