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AUTHORITY
USAMRMC ltr, 26 Aug 2002

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE October 1998	3. REPORT TYPE AND DATES COVERED Annual (15 Sep 97 - 14 Sep 98)	
4. TITLE AND SUBTITLE Risk Factors for Chorioamnion Infection and Adverse Pregnancy Outcome Among Active-Duty Military Women and Dependent Women		5. FUNDING NUMBERS DAMD17-95-1-5054	
6. AUTHOR(S) Gail H. Cassell, Ph.D.			
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Alabama at Birmingham Birmingham, Alabama 35294-0111		8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES			
1 9990610135			
12a. DISTRIBUTION / AVAILABILITY STATEMENT Distribution authorized to U.S. Government agencies only (proprietary information, October 1998). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.		12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) Cervicovaginal ureaplasma infection alone is not predictive of preterm birth. Only a subpopulation of women infected in the lower genital tract are at risk for chorioamnion invasion and premature birth. The major goal of the proposed study is to identify microbiologic factors that predispose to and/or predict chorioamnion invasion and premature birth. This study will determine if the presence of bacterial vaginosis (BV) is a risk factor for ureaplasma invasion of the chorioamnion. 3,464 women have been enrolled to date. Vaginal cultures from all of these women have been assessed for <i>Ureaplasma urealyticum</i> (UU) colonization and gram stains have been assessed for BV. Data sheets from 2,205 women (prenatal visit) have been scanned and the data analyzed. Prenatal screens yield 1176/2190 or 54% culturally positive for UU and 384/2,101 or 18.3% of the gram stains are positive for BV. At delivery (388 women meeting study criteria for placental cultures including multiple births), the isolation rate of UU from the vagina is 53% regardless of delivery route. The isolation rate of UU from placental tissues is 9% from Cesarean section (C-section) deliveries and 15 % from vaginal deliveries. The isolation rate of UU from amniotic fluid is 18.5% and from infant's nasal passages is 14% from C-section deliveries and 27% from vaginal deliveries. Gram stains for BV assessment at delivery is 17.9%.			
14. SUBJECT TERMS Defense Women's Health Research Program		15. NUMBER OF PAGES 21	
		16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Limited

GRANT NUMBER DAMD17-95-1-5054

TITLE: Risk Factors for Chorioamnion Infection and Adverse Pregnancy Outcome Among Active-Duty Military Women and Dependent Women

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CONTRACTING ORGANIZATION: University of Alabama at Birmingham
Birmingham, Alabama 35294-0111

REPORT DATE: October 1998

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

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FOREWORD

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☒ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

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PI Signature

Date

UAB THE UNIVERSITY OF
ALABAMA AT BIRMINGHAM

Department of Microbiology
Diagnostic Mycoplasma Laboratory

October 13, 1998

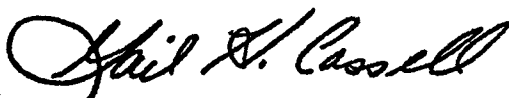
Judy Pawlus
Office of the Deputy Chief of
Staff for Information Management
U.S. Army Medical Research and Material Command
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Ms. Pawlus:

The data presented in this report is preliminary. It is my request that this data not be published or presented at this time. This is a very worthwhile study and much information is being collected on this military population. The data collected will be very beneficial to the military but I feel that it is too early in the data analysis to make any conclusions.

I appreciate the opportunity that we have had in these collaborative efforts with the Navy and look forward to seeing the completed analysis that will be generated from this study. Thank you for your consideration of this request.

Sincerely,



Gail H. Cassell, Ph.D.
Professor, Dept. of Microbiology

TABLE OF CONTENTS

FRONT COVER	1
SF 298	2
FOREWORD	3
LETTER OF REQUEST	4
TABLE OF CONTENTS	5
INTRODUCTION	6
BODY	6
CONCLUSION	11
REFERENCES	14
APPENDIX I	16
APPENDIX II	19

INTRODUCTION:

Women are playing increasing roles in active duty military service and suffering unexplained adverse outcomes of pregnancy. In the Navy, up to 20% of enlisted women become pregnant each year and nearly 15% of these pregnancies suffer adverse effects. The percentage is in excess of that experienced in most other U.S. female populations and despite a number of preliminary investigations, the difference does not appear to be related to environmental exposures.

Some of the traditional factors associated with adverse outcomes of pregnancy such as limited access to prenatal care or poor nutritional status are not operative among naval personnel, nonetheless at least 10% of Navy live births are premature (< 37 weeks gestation) or low birth weight. In addition, previous studies have indicated among pregnant, enlisted women, spontaneous abortions occur in 9.9%, 2.7% of pregnancies are ectopic and 1.5% result in fetal death (0.7% early and 0.8% late). Bacterial infections of the lower genital tract may in part explain poor pregnancy outcome.

Preterm birth complicates 8-10% of all pregnancies in the U. S. and is the leading cause of infant morbidity and mortality in the U.S. We have previously shown that *Ureaplasma urealyticum* (*Uu*) is the single most common microorganism isolated from the chorioamnion of women in spontaneous labor with intact membranes and in whom there are no chances for cervicovaginal contamination of the placenta (i.e. they delivered by cesarean section with intact membranes). Furthermore, ureaplasma infection of the chorioamnion in the absence of other bacteria was associated with birth < 37 weeks even after multifactorial analysis to adjust for labor and other obstetric and demographic factors that could confound the association. Infection was inversely related to gestational age and birth weight. Other related studies indicate that ureaplasma infection is a significant cause of respiratory disease, meningitis and death in very low birth weight infants.

The major goal of the proposed study is to define those women who are at risk for adverse pregnancy outcomes and to determine whether chorioamnion infection, in particular infection with *Uu*, is associated with these outcomes, specifically premature birth. This will allow us to identify factors that may predict invasion and premature birth. We will determine if the presence of BV is a risk factor for ureaplasma invasion of the chorioamnion. Potential confounders of these data will be controlled through multivariate analyses. They include the presence of other sexually transmitted pathogens, in particular *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, Group B streptococci, *Trichomonas vaginalis*, *Mycoplasma hominis*, and *Mycoplasma genitalium*.

BODY:

Experimental methods to be used in this study are identical to those detailed in the original proposal.

During the last year, we have enrolled an additional 1,709 patients for a total of 3,464. Our enrollment rate has decreased but the overall number of patients seen has increased since we added self-swabbing of patients to the protocol as discussed in last year's report. We are

constantly looking for ways to improve the numbers seen and to increase the numbers of those consenting. Enclosed in Appendix I is an example of a patient brochure that is given to each patient seen in the prenatal clinic prior to being seen by the study enroller. We felt that this was a good way to introduce the study to patients and to generate interest. Also included in Appendix I are samples of bookmarks with helpful pregnancy tips that are given to each patient that enrolls.

Demographics of the enrollees that have been analyzed to date (those attending the Naval Medical Center San Diego Obstetrics clinic for their first pre-natal visit) and consenting to participate in the UAB Study are demonstrated below:

Age Range	14-46		
		N	(%)
Race			
	White	1171	(53.4)
	Asian/PI	318	(14.5)
	Black	303	(13.8)
	Spanish/Hispanic	289	(13.2)
	Other	87	(4.0)
	Eskimo/Aleut./American Indian	16	(0.7)
	Multiple race	10	(0.5)
Military Status			
	Navy	437	(21.9)
	Retired Military	17	(0.9)
	Marine	18	(0.9)
	Reserve	12	(0.6)
	Army	1	(0.1)
	Public Health	1	(0.1)
	National Guard	1	(0.1)
	Civilian	1511	(75.6)

Of the 2,205 women that have enrolled in the UAB study and whose outcome data have been analyzed, 2,101 have slides that were analyzed for BV by the Nugent Gram Stain method. 384/2101 (18.3%) are positive for BV (a score of ≥ 7). Trichomonas has been isolated from 19 patients (0.9%). These were consistent with last year's report. *Ureaplasma urealyticum* (Uu) and Mycoplasma species (Myco sp.) have been isolated from 1234/2190 (56.3%) and 226/2190 (10.3%) respectively. A breakdown of results are found in Table 1.

Table 1
***Ureaplasma urealyticum*, Mycoplasma species and Bacterial Vaginosis**
Pre-natal Screens
N=2,101

	BV only	Uu only	MYCO SP only	NEG	BV+Uu	BV+MYCO SP	BV+Uu+MYCO SP	Uu+MYCO SP	OVG*
N	85	890	8	750	139	13	147	58	11
%	4.0	42.4	0.4	35.7	6.6	0.6	7.0	2.8	0.5

*Overgrown with bacteria

A subset of these patients were recently analyzed for a presentation at this year's American College of Obstetrics and Gynecology, The Armed Forces district meeting in Kissimmee, FL being held October 18-21, 1998. This project was to examine the prevalence of BV in active duty and non-active duty women attending the prenatal clinic at NMCS D. A copy of the poster can be found in Appendix II.

This study has afforded us the opportunity to follow a large cohort of women as to their delivery outcome. In addition to the women that meet our study criteria and have their placentas, etc. submitted for culture workup, we have collected outcome data on the delivery status of all women that have enrolled in the UAB study at their prenatal visit. This information has been crucial in determining the overall pregnancy outcomes for this population. The outcomes of those deliveries are summarized in Table 2. Flowcharts describing the types of delivery of this patient population at the Naval Medical Center San Diego (NMCS D) are found in Figures 1 and 2.

Table 2
UAB Study Pregnancy Outcome
N=1851

Full Term Deliveries > 37 weeks gestation	1479
Preterm Deliveries 25-36 weeks gestation	157
IUFD	18
SAB	190
Abortion/TAB	7

By following these outcomes, we have a better understanding of the population that we are studying. We have looked closer at those women whose outcomes were Intra-uterine fetal demise (IUFD), spontaneous abortion (SAB) and preterm deliveries. As compared to term deliveries, the infection status is found in Table 3.

Table 3
Cultural Status of Prenatal Patients

	BV only	Uu only	MYCO SP only	BV + Uu	BV + Uu+MYCO SP	BV + MYCO SP	Uu+MYCO SP	NEGATIVE
IUFD (N=18)	0 (0%)	6 (33.3%)	0 (0%)	1 (5.5%)	4 (22.2%)	0 (0%)	0 (0%)	7 (38.9%)
SAB (N = 158)	9 (5.7%)	65 (43.6%)	2 (1.3%)	7 (4.7%)	13 (8.7%)	3 (2.0%)	4 (2.7%)	55 (36.9%)
Preterm (N=150)	4 (2.7%)	64 (42.7%)	1 (0.7%)	11 (7.3%)	12 (8.0%)	1 (0.7%)	6 (4.0%)	50 (33.3%)
Term (N=1447)	63 (4.35)	624 (42.9%)	2 (0.1%)	97 (6.7%)	89 (6.1%)	6 (0.4%)	35 (2.4%)	531 (36.5%)

These groups will be very interesting to watch as our overall numbers increase.

Figure 1

TOTAL DELIVERIES

DELIVERY TYPE BREAKDOWN

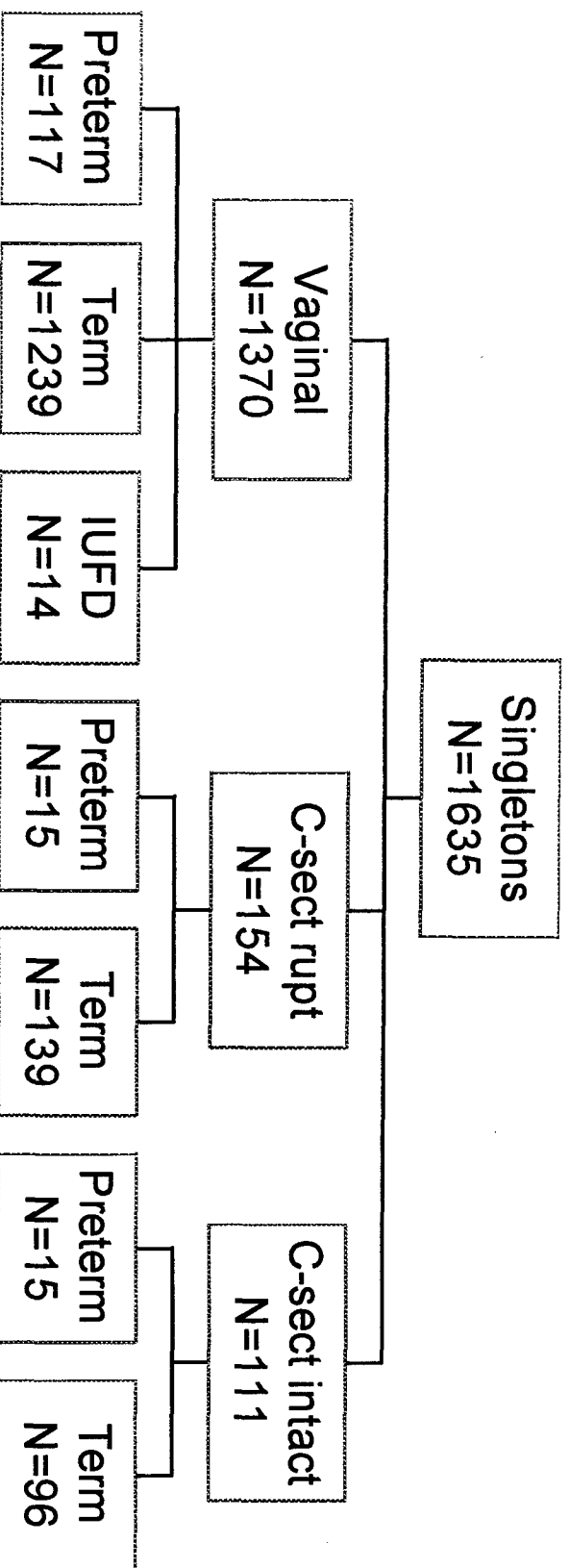
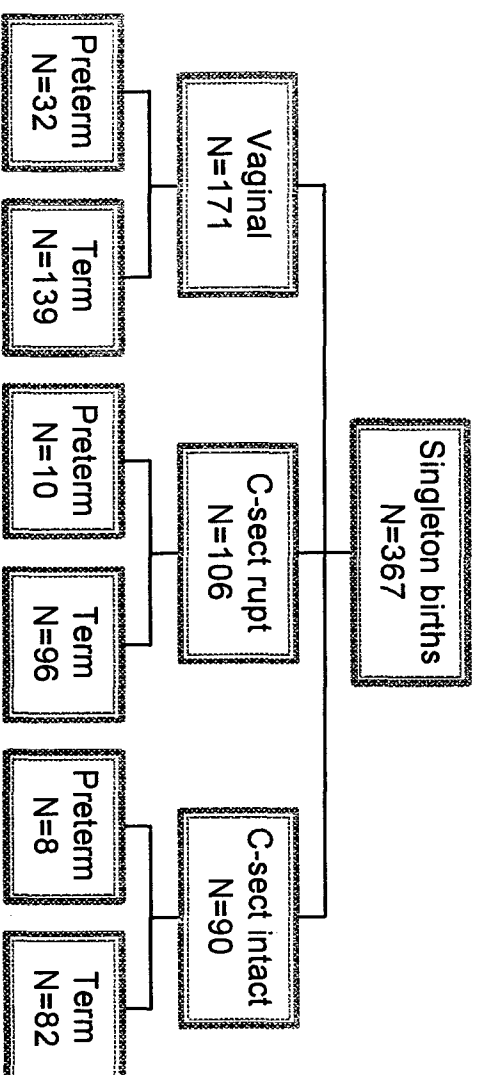


Figure 2

PRENATAL/DELIVERY COMPLETED DATA SET



The current C-section rate of delivery is between 14% and 18%. This rate is much lower than the predicted rate from which we based our original proposal. We have since changed our protocol to include all C-section deliveries regardless of membrane status and have received approval to culture the placentas from all preterm deliveries (≤ 34 weeks). To date, we have analyzed the cultural data from 367 women (singleton births only) that have met study criteria i.e. vaginal swabs prior to delivery for BV assessment and *Ureaplasma urealyticum* colonization, placenta and amniotic fluid for culture of aerobes, anaerobes and ureaplasma and mycoplasma, and infant nasal cultures for ureaplasma and mycoplasma colonization. Cultures for aerobes and anaerobes are processed at NMCS D within an hour of delivery. Cultures for ureaplasma and mycoplasma are frozen at -70°C , batched, and sent to the UAB reference laboratory on dry ice monthly. Vaginal cultures collected just prior to delivery were positive for *Uu* in 55% of the patients delivering by singleton births. Two patients had mycoplasma species only (0.06%) and there were 20 patients that were culturally positive for both *Uu* and mycoplasma species (5.7%). BV assessment has been performed on 357 slides submitted for analysis. 64/357 (17.9%) were graded as positive and 293/357 (82.1%) were considered to be negative. *Uu* was isolated from the placental tissues in pure culture in 22/367 (6%) of the patients and mixed with other bacteria in 22/367 (6%). The bacterial results are further described in Figures 3 and 4.

CONCLUSION:

Through our efforts, the population is well defined and enrollment is increasing. However, at delivery there have been only 90 cesarean sections with intact membranes to date and only 15 were preterm birth. Due to this small number, our overall goal to concentrate on just this population has changed. Because we had the foresight to collect the outcome data on all women enrolling in the UAB study, we now have some very interesting data that will benefit the attending physicians at NMCS D concerning their population. By adding all women that transfer in at NMCS D for preterm delivery (≤ 34 wks) and consent to participate and adding all vaginal preterm deliveries of women previously enrolled in the UAB study, we hopefully will be able to better understand the causal role of these preterm births. We will continue to enroll patients through April of 1999 although in our original proposal we were not going to enroll patients in the fourth year. We feel that it is necessary to continue enrollment trying to reach a total of 5,000 women. This work will be funded by outside sources other than DOD funds.

Figure 3

**PRENATAL/DELIVERY GROUP
BACTERIAL ASSESSMENT OF PLACENTAL TISSUE
BY DELIVERY TYPE**

	UU ONLY	UU + BC	BC ONLY	NEG	ANY UU	ANY BC	ANY POS
VAG DEL. N = 171	12	14	63	82	26	76	89
C-SECT. RUPT. N= 106	10	8	19	69	18	27	37
C-SECT. INTACT. N = 90	0	0	11	79	0	11	11

Figure 4

NASAL PASSAGE CULTURES OF INFANTS BORN TO STUDY PATIENTS (N = 367)

* NO BACTERIAL DATA (7 MISSING)

VAGINAL DEL. N = 171	UU ONLY	MYCO ONLY	UU+MYCO	NEG	MISSING
	46	3	1	120	1

C-SECT. RUPT. DEL. N = 106	UU ONLY	MYCO ONLY	UU+MYCO	NEG	MISSING
	27	0	0	76	3

C-SECT. INTACT DEL. N = 90	UU ONLY	MYCO ONLY	UU+MYCO	NEG	MISSING
	0	0	0	87	3

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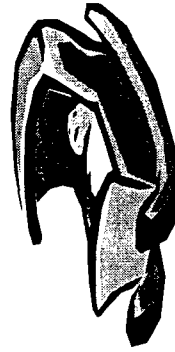
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APPENDIX I

VAB Study

CHORIOAMNION INFECTION STUDY



FOR HEALTHY MOTHERS AND BABIES

The Naval Medical Center San Diego (NMCSD) wishes to provide the best obstetrical care possible to military families. For this reason NMCSD is collaborating with the University of Alabama at Birmingham and the Naval Health Research Center to investigate reports that bacterial infections cause pregnancy complications which may include premature delivery, miscarriage, stillbirth and possibly infection in the newborn infant.

The VAB Study may help you and will ultimately help women have healthier babies in the future.

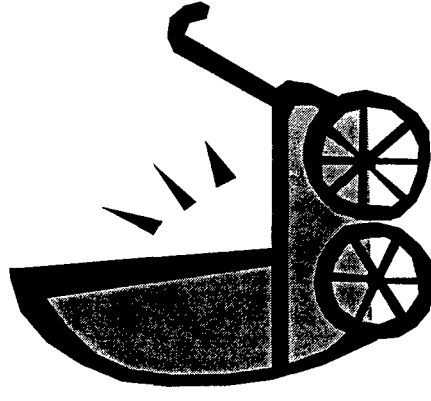
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Robert L. Goldenberg, MD

Special thanks to the staff of Labor & Delivery, NICU and
Prenatal Registration at NMCSD

VAB STUDY

CHORIOAMNION INFECTION STUDY



FOR HEALTHY MOTHERS AND BABIES

A JOINT RESEARCH PROJECT BETWEEN
UNIVERSITY OF ALABAMA AT BIRMINGHAM
NAVAL MEDICAL CENTER SAN DIEGO AND
THE NAVAL HEALTH RESEARCH CENTER

HOW DOES MY PARTICIPATION HELP?

By taking a few extra minutes to participate, you may make a tremendous contribution to the future understanding of bacterial infections and their effect on pregnancy and the health of the unborn or newborn infant.



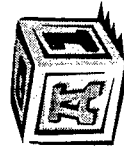
WHAT WILL I HAVE TO DO IF I CHOOSE TO PARTICIPATE?

If you choose to participate, at today's visit you will be asked to:

- ★ consent to participate
- ★ fill out a brief questionnaire
- ★ have a small amount of blood drawn during your routine lab draw
- ★ obtain vaginal self-swabs before collecting your routine urine sample
- ★ there are no extra visits necessary

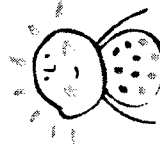
Then, when you deliver, you will be asked to:

- ★ have a small amount of blood drawn during your routine lab draw
- ★ have vaginal swabs obtained by your Labor & Delivery nurse, doctor or midwife



WILL THE INFORMATION ABOUT ME BE KEPT CONFIDENTIAL?

Yes, all information about you and your baby is kept confidential.

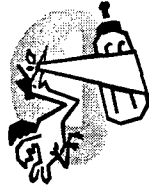


IS THERE ANY RISK TO MY BABY OR ME?

No, your participation in this study will not interfere with or delay the normal care you or your baby receive and will not increase you or your baby's discomfort.

UAB STUDY

CHORIOAMNION INFECTION
STUDY



FOR HEALTHY MOTHERS
AND BABIES

You have the opportunity to participate in this very important study at the Naval Medical Center San Diego (NMCSD). After registering for prenatal care you will have the opportunity to speak with the UAB Study Nurse. She will answer any questions you may have about the study and ask you to participate.

If you would like more information about the UAB Study, you may speak with the UAB Study nurse in



the prenatal clinic at
NMCSD or call 532-9243.



UAB STUDY

HEALTHY PREGNANCY TIPS

- ** Receive prenatal care early and regularly during your pregnancy
- ** Take care of your needs for rest, exercise, and good nutrition

AVOID DURING PREGNANCY

- ** ALCOHOL can cause serious harm to your developing baby including mental retardation
- ** SMOKING deprives your baby of necessary oxygen
- ** DRUGS like marijuana, cocaine and crack, go directly into your baby's body
- ** Talk to your health care provider before taking any over-the-counter MEDICATIONS or PRESCRIPTION DRUGS because they may be harmful to your baby
- ** UNCOOKED MEAT and CAT FECES can transmit a disease called Toxoplasmosis; thoroughly cook your meat and avoid handling cat litter while you are pregnant

- ** Avoid excessive CAFFEINE

Thank you for participating
in the UAB Study
(619) 532-9242



UAB STUDY

HEALTHY PREGNANCY TIPS

- ** Receive prenatal care early and regularly during your pregnancy
- ** Take care of your needs for rest, exercise, and good nutrition

AVOID DURING PREGNANCY

- ** ALCOHOL can cause serious harm to your developing baby including mental retardation
- ** SMOKING deprives your baby of necessary oxygen
- ** DRUGS like marijuana, cocaine and crack, go directly into your baby's body
- ** Talk to your health care provider before taking any over-the-counter MEDICATIONS or PRESCRIPTION DRUGS because they may be harmful to your baby
- ** UNCOOKED MEAT and CAT FECES can transmit a disease called Toxoplasmosis; thoroughly cook your meat and avoid handling cat litter while you are pregnant

- ** Avoid excessive CAFFEINE

Thank you for participating
in the UAB Study
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APPENDIX II



Prenatal Prevalence of Bacterial Vaginosis Among Military Beneficiaries

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Revised Abstract

Bacterial vaginosis has been associated with preterm labor and other adverse pregnancy outcomes. The presence or absence of bacterial vaginosis (BV) was evaluated for 2,202 pregnant women at Naval Medical Center San Diego (NMCSD) who had enrolled in a prospective epidemiological study of chorioamnion infection from June 1996 to January 1998. The use of self-obtained vaginal specimens was validated so that during prenatal screening these women were able to perform vaginal self-swabs for the detection of BV. Data collection and subject follow-up continues. Preliminary prenatal screening data reveal that these military beneficiaries have a normal prevalence of BV, 18% using Nugent Gram stain method.

A total population of 2,202 were enrolled with complete covariate data for 1,888 women. Active duty women were more likely to have BV:

	Active duty (n=428)	Non-active (n=1,460)	Odds Ratio (95%CI)
BV	23%	17%	1.45 (1.11-1.90)

However, after adjusting for marital status and age, there was no appreciable difference between the prevalence of BV among active duty and non-active duty military beneficiaries.

Objective

The prevalence of bacterial vaginosis among military beneficiaries seeking prenatal care at the NMCSD was examined comparing active duty women to the non-active duty women.

Methods

- The women examined for bacterial vaginosis were enrolled in the UAB Chorioamnion Infection Study
- All women seeking prenatal care at the NMCSD were eligible to participate
- Those consenting: answered a questionnaire, had serum drawn, and self-obtained vaginal swabs after their registration for first prenatal visit
- 2,202 women gave informed consent
- Women were evaluated for bacterial vaginosis using the Nugent Method**

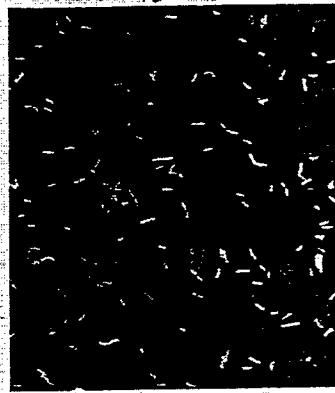
Validation of Self-Obtained Specimens

- In a previous abstract, self-obtained specimens were compared to clinician-obtained specimens (n=53 pairs)
- Bacterial vaginosis evaluation (96% agreement)
 - Pairs agreed upon: 39 normal, 3 intermediate, 9 positive
 - Pairs discordant: 2
 - Clinician-obtained specimens interpreted as intermediate
 - Self-obtained specimens interpreted as normal

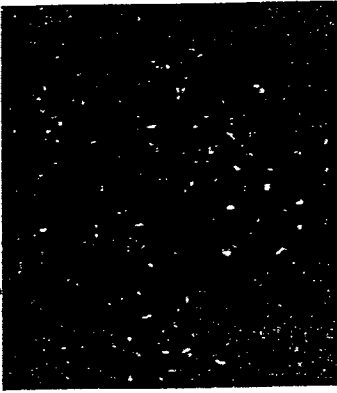
Gram Stain Interpretation of Bacterial Vaginosis Smears by Nugent Method**

- Evaluated for the presence and number of Lactobacillus morphotypes (*Lactobacillus* species), *Gardnerella* & *Bacteroides* species morphotypes, and curved gram-variable rods (*Mobiluncus* species)
- Scored 0-10 points: 0-3 "normal flora"
 - 4-6 intermediate
 - 7-10 bacterial vaginosis

Slide of "Normal" Flora



Slide of Bacterial Vaginosis



Results

Table 1.

BV Results	Normal & Intermediate	Bacterial Vaginosis
Active duty (N=428)	77%	23%
Non-active duty (N=1,460)	83%	17%

*Chi square test

It was observed that active duty women had a higher prevalence of BV upon enrollment by gram stain interpretation (Table 1). However, when adjusted for marital status and age, there was no statistically significant difference between active-duty and non-active duty women (Table 2).

Table 2.

	Odds Ratio*	Wald 95% Confidence Limits
Active duty status	1.31	(0.99 - 1.74)
Age	0.81	(0.73 - 0.92)
Marital status	0.87	(0.63 - 1.23)

*Logistic regression

Discussion

- The prevalence is comparable to the national average
- These data illustrate the difficulty in comparing the prevalence of a clinical condition between populations which differ by important confounding risk factors.

Conclusion

In the prenatal clinic at NMCSD, BV was not significantly more prevalent among active duty women as compared to non-active duty women



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

26 Aug 02

MEMORANDUM FOR Administrator, Defense Technical Information
Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir,
VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

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