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Naval Health Research Center

Report No. 09-18

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Health Outcomes among Infants Born to Women Deployed to United States Military Operations during Pregnancy

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Received 28 May 2010; Revised 2 September 2010; Accepted 3 September 2010

BACKGROUND: Military professionals who deploy to combat operations may encounter hazards that could adversely affect reproductive health. Pregnant women are generally exempt from deployment to military operations, however, exposures to such environments may inadvertently occur. We investigated whether maternal deployment during pregnancy was associated with adverse health outcomes in infants. **METHODS:** The United States Department of Defense Birth and Infant Health Registry identified infants born to military service women between 2002 and 2005, and defined their health outcomes at birth and in the first year of life. Multivariable modeling was applied to investigate preterm birth and birth defects among infants, based on maternal deployment experience during pregnancy. **RESULTS:** Among 63,056 infants born to military women from 2002 to 2005, 22,596 were born to women with deployment experience in support of the current military operations before, during, or after their pregnancy. These included 2941 infants born to women who appeared to have been deployed some time during their first trimester of pregnancy. Compared to infants born to women who deployed at other times, or never deployed, exposed infants were not more likely to be born preterm, diagnosed with a major birth defect, or diagnosed with a malignancy. **CONCLUSIONS:** In this exploratory analysis, infants born to women who inadvertently deployed to military operations during their pregnancy were not at increased risk of adverse birth or infant health outcomes. Future analyses should examine outcomes related to specific maternal exposures during deployment, and outcomes among the growing number of infants conceived after deployment. *Birth Defects Research (Part A) 91:117–124, 2011. Published 2010 Wiley-Liss, Inc.*[†]

Key words: congenital abnormalities; military personnel; reproductive history; women's health

INTRODUCTION

After past military combat operations, including the Vietnam War and the 1991 Gulf War, some returning veterans reported reproductive health problems they attributed to exposures faced during wartime deployment. Concerns have included fertility problems, pregnancy losses, and having infants with birth defects (Araneta et al., 2004; Aschengrau and Monson, 1990; Briggs, 1995; Cowan et al., 1997; Doyle et al., 2004; Doyle et al., 2006; Kang et al., 2000; Kang et al., 2001; Ngo et al., 2006; Stellman et al., 1988; Wells et al., 2006). More recently, the deployments of U.S. troops in support of the wars in Iraq and Afghanistan have heightened reproductive health concerns among service members and their families. In fact, media reports have indicated some service members have elected to store their semen prior to deployment because of concerns about their reproduc-

tive health after working in combat operations (Alvord, 2003; Kelly, 2003).

Young adults deployed to military operations may encounter a variety of hazards that may adversely affect

This represents report 09-19, supported by the U.S. Department of Defense, under work unit no. 60504.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the U.S. Department of the Navy, U.S. Department of Defense, or the U.S. Government. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocol NHRC.2007.0002).

[†]This article is a U.S. Government work and, as such, is in the public domain in the United States of America.

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Published online 1 December 2010 in Wiley Online Library (wileyonlinelibrary.com).

DOI: 10.1002/bdra.20746

reproductive health. Several environmental hazards were identified as specific reproductive health concerns in the 1991 Gulf War theater (Arfsten et al., 2001; Reutman et al., 2002; Wheeler et al., 1994). Measures intended to prevent illness in troops, including pesticides, prophylactic medications, and some immunizations, have also been considered potential reproductive health hazards (Hanke and Jurewicz, 2004; Jacobson et al., 2008a; Ryan et al., 2008a; Ryan et al., 2008b; Ryan and Seward, 2008). The spectrum of reproductive health concerns includes effects among both men and women, and outcomes ranging from fertility challenges to infant health problems. Most studies have evaluated infant health outcomes, including birth defects, in part because such outcomes are visible and definable with fairly well-established expected prevalence rates in the general population (Briggs, 1995; Correa-Villaseñor et al., 2003; Cowan et al., 1997; Doyle et al., 2004; Doyle et al., 2006; Ngo et al., 2006).

The timing of any exposures of concern related to a subsequent health outcome is critical in evaluating the strength of such relationships. Most studies of pregnancy outcomes among military troops have examined only pregnancies conceived after deployment. Studies examining outcomes related to exposure in the first trimester of pregnancy, the most vulnerable period of fetal development, have generally been limited by small numbers of exposed pregnancies. This is particularly true regarding deployment-related exposures, since U.S. military policy precludes operational deployment among pregnant women. One survey study of 409 women who appeared to have been inadvertently deployed during pregnancy in the 1991 Gulf War did not demonstrate any significant increases in adverse pregnancy outcomes (Araneta et al., 2004).

An increasing number of young women have been deployed to military operations since 2001. Although U.S. military policy still precludes deployment during pregnancy, pregnancies that are recognized after deployment or conceived in theater will be exposed to the operational environment. These pregnancies are of special interest in evaluating the potential reproductive health effects of military occupational exposures. The U.S. Department of Defense (DoD) Birth and Infant Health Registry was established in the 1990's to objectively evaluate these important issues (Ryan et al., 2001).

MATERIALS AND METHODS

Population

Nearly 100,000 infants are born to U.S. military families each year (Ryan et al., 2001). DoD-sponsored births occur in all 50 states, the District of Columbia, and in more than 20 foreign countries. The cohort for these analyses included infants born in the calendar years 2002 through 2005, to military women with adequate demographic information to uniquely identify them. Same-sex multiples are excluded from the cohort because unique identifiers may not be assigned until several days after birth, making accurate assignment of outcomes difficult. The primary exposure of interest for this study was maternal deployment within the first trimester of pregnancy. The primary referent population included infants born to mothers who deployed any time after September 10, 2001, but not during the first trimester of pregnancy. This

work was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocol NHRC. 2007.0002).

Data Sources

The DoD Birth and Infant Health Registry compiles data from multiple sources to capture birth and infant health outcomes in the first year of life (Ryan et al., 2001). Diagnostic data, based on the *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM), are obtained by accessing electronic inpatient and outpatient medical records from the following sources: Standard Inpatient Data Record, which contains one record for each inpatient health care encounter at a military treatment facility; Standard Ambulatory Data Record, which contains one record for each outpatient health care encounter at a military treatment facility; and TRICARE encounter data, both inpatient and outpatient, which contain one record for each health care encounter at a civilian facility that is submitted for reimbursement to the military health care system.

Military personnel rosters were used to assess maternal age, maternal race/ethnicity, maternal marital status, maternal branch of service, maternal rank, and maternal military occupation. Deployment dates to military operations between September 2001 and March 2008 were determined using military electronic data from the Defense Manpower Data Center in Monterey Bay, California.

Outcomes

Estimated gestational age (EGA) for each infant was defined using ICD-9-CM codes; specifically, by code 765.2x, with the maximum end of each range assigned as the infant's EGA at birth. For code 765.29, EGA of 40 weeks was assumed. If a 765.2x code was not assigned, then 765.0x and 765.1x codes were used to assign EGA at birth, where the shorter EGA was assumed to be correct if both codes were present. Infants assigned 765.0x were assumed to have reached EGA of 28 weeks, and infants assigned 765.1x were assumed to have reached EGA of 36 weeks. The maximum end of each gestational age range for preterm infants was applied in recognition that the distribution of actual gestational ages is skewed toward the overall mean (40 weeks). Applying the maximum end of the gestational age range also allowed the largest possible time window for maternal exposure in each pregnancy to be included. In the absence of the aforementioned codes, EGA of 40 weeks was assumed. If more than one 765.2x code existed for a single infant, the most recent code assigned was used, and the shorter EGA was used if multiple codes appeared on the same day. Infants born to mothers who deployed after EGA of 28 weeks were excluded from the analyses of preterm delivery, since these infants would not have had the opportunity to be born under the "extreme preterm" definition after exposure. Additionally, multiple births were excluded from the analysis of preterm delivery.

Major birth defects were defined by the ICD-9-CM case definitions of the National Birth Defects Prevention Network (Correa-Villaseñor et al., 2003; Sever, 2004). Cases of atrial septal defect (745.5x) and patent ductus arteriosus (747.0x) in preterm infants were not included as birth

defects, in accordance with Metropolitan Atlanta Congenital Defects Program guidelines.

Malignant neoplasm cases among infants were defined by ICD-9-CM codes in the range 140.xx through 208.xx. Inpatient care was required to be considered a malignancy (rather than a rule-out diagnosis), and a sample of cases was further validated by clinician review (authors M.A.K.R. and A.M.S.C.) of all available medical records.

Statistical Analyses

Analyses included descriptive investigations of maternal demographic and occupational characteristics stratified by deployment status. Univariate analyses, including chi-square tests, were performed to assess the significance of associations between the outcomes of interest and deployment status. Exploratory model analyses were completed for the outcomes of birth defects and preterm birth to assess regression diagnostics, significant associations, collinearity, and possible confounding, while adjusting for all other variables in the model. Malignant neoplasms were investigated in this population and were found to be extremely rare, thus preventing statistical analyses and inclusion in reported analyses.

Multivariable logistic regression models were used to estimate the adjusted odds of preterm birth and birth defects among infants born to deployed mothers. Evaluation of preterm birth as a polychotomous outcome was conducted using three levels: extreme preterm birth (EGA of ≤ 28 weeks), preterm birth (EGA of >28 – 36 weeks), and full-term birth (EGA of >36 weeks). Multivariable logistic regression models were developed for the outcome of any birth defect, and specific birth defects with five or more cases in both the exposed and referent groups. For rare outcomes, the odds ratio was estimated using exact logistic regression. Bonferroni adjustment for multiple comparisons was applied to confidence limits in models of specific defects. The models used generalized estimating equations to account for correlated outcomes among multiple births (Liang and Zeger, 1986); such births included siblings from different pregnancies and twins. When available, models were adjusted for multiple birth, infant gender, maternal age, maternal race/ethnicity, maternal marital status, maternal branch of military service, maternal rank, maternal military occupation, and maternal duty status. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC).

The primary analysis examined infants born to mothers deployed in the first trimester of pregnancy compared to infants born to women who deployed during the observation period but not in the first trimester of pregnancy. Alternative models were developed with these referent groups: infants born to mothers who deployed only post-pregnancy, and infants born to mothers who were never deployed. In the alternative models, exposure groups included infants born to mothers who deployed prepregnancy and infants born to mothers who appeared to have been deployed in late pregnancy; one model was developed to compare infants of ever-deployed mothers with infants of never-deployed mothers. Finally, because of data challenges that precluded capture of all multiple births, the primary analysis of birth defect outcomes was re-examined with only singleton infants included.

RESULTS

Among 63,056 infants born to military women from 2002 to 2005, 22,596 were born to women with operational deployment experience in support of the wars in Iraq and Afghanistan before, during, or after their pregnancy. These included 2941 infants born to women who seemed to have been deployed some time during the first trimester of pregnancy (Table 1). There were 19,655 infants born to women who deployed in support of military operations outside of the first trimester; 8092 infants were born to women who deployed before pregnancy, 145 infants were born to women who deployed late in pregnancy, and 11,418 infants were born to women who deployed after giving birth. There were 40,460 infants born to military women in 2002 to 2005 who had no record of deploying. Compared to ever-deployed mothers, never-deployed mothers tended to be older, white, married, officers, and working in military health care occupations.

Infants born to women who deployed during pregnancy were not at increased odds of being born preterm or extremely preterm when compared to infants born to women who deployed before or after pregnancy (Table 2). Additionally, when comparing infants born to women who deployed during pregnancy with those born to women who never deployed or deployed only after pregnancy, we did not observe significant increased odds for preterm or extreme preterm birth.

Approximately 3.5% of infants in this cohort were diagnosed with birth defects in the first year of life. In multivariable modeling, non-singleton infants, male infants, and infants born to mothers aged 35 years or older were significantly more likely to have birth defects (Table 3). The prevalence of birth defects among infants born to women who were deployed to military operations in the first trimester of pregnancy was not statistically significantly different from the rate in infants in the primary referent group. When alternative referent groups were considered, including infants born to women who deployed only after pregnancy or infants born to never-deployed women, no statistically significant differences in the prevalence of birth defects was found (Table 4). Results were unchanged when the primary analyses were restricted to only singleton infants.

Specific types of birth defects among infants born to women who deployed during the first trimester were compared to infants born to women with other deployment experiences (Table 5). The prevalence of hydrocephalus without spina bifida was greater among infants born to women who deployed in early pregnancy, but the difference was not statistically significant when adjustment for multiple comparisons was applied.

Very few infants were diagnosed with malignant neoplasms requiring hospitalization in the first year of life among this cohort. Although multivariable statistical modeling was not performed for these rare outcomes, no increased rates of malignancies were observed among infants born to women who had deployed during their pregnancy (Table 1).

There were 469 infants who would have been included in the primary analysis, i.e., born to military women with deployment experience in this period and having clearly defined infant health records, but who were excluded from analyses because of incomplete maternal demo-

Table 1
Characteristics of Infants Born to Military Women, 2002 to 2005, by Maternal Deployment Experience

	Never deployed n = 40,460	Deployed prepregnancy n = 8092	Deployed in 1st trimester n = 2941	Deployed in late pregnancy n = 145	Deployed postpregnancy n = 11,418	Total n = 63,056
Infants with birth defects	1466 (3.6)	285 (3.5)	113 (3.8)	4 (2.8)	378 (3.3)	2246
Infants with malignancies	10 (0.0)	6 (0.1)	0 (0.0)	0 (0.0)	3 (0.0)	19
Gestational age at birth						
Full-term	37,360 (92.3)	7482 (92.5)	2689 (91.4)	137 (94.5)	10,586 (92.7)	58,254
Preterm	2757 (6.8)	540 (6.7)	221 (7.5)	8 (5.5)	741 (6.5)	4267
Extreme preterm	343 (0.8)	70 (0.9)	31 (1.1)	0 (0.0)	91 (0.8)	535
Infant plurality						
Singleton	40,057 (99.0)	8015 (99.0)	2908 (98.9)	144 (99.3)	11,295 (98.9)	62,419
Multiple	403 (1.0)	77 (1.0)	33 (1.1)	1 (0.7)	123 (1.1)	637
Infant gender						
Female	19,917 (49.2)	3905 (48.3)	1400 (47.6)	65 (44.8)	5563 (48.7)	30,850
Male	20,543 (50.8)	4187 (51.7)	1541 (52.4)	80 (55.2)	5855 (51.3)	32,206
Maternal age at birth						
<35 years	37,335 (92.3)	7660 (94.7)	2824 (96.0)	138 (95.2)	10,833 (94.9)	58,790
≥35 years	3125 (7.7)	432 (5.3)	117 (4.0)	7 (4.8)	585 (5.1)	4266
Maternal race/ethnicity						
White	20,853 (51.5)	3664 (45.3)	1210 (41.1)	65 (44.8)	4741 (41.5)	30,533
Black	11,655 (28.8)	2615 (32.3)	1117 (38.0)	54 (37.2)	4258 (37.3)	19,699
Hispanic	4647 (11.5)	1059 (13.1)	386 (13.1)	15 (10.3)	1401 (12.3)	7508
Asian	1787 (4.4)	415 (5.1)	116 (3.9)	8 (5.5)	626 (5.5)	2952
Other/unknown	1518 (3.8)	339 (4.2)	112 (3.8)	3 (2.1)	392 (3.4)	2364
Maternal marital status						
Married	28,552 (70.6)	5442 (67.3)	1509 (51.3)	73 (50.3)	7507 (65.7)	43,083
Unmarried	11,908 (29.4)	2650 (32.7)	1432 (48.7)	72 (49.7)	3911 (34.3)	19,973
Maternal service branch						
Army	12,791 (31.6)	2026 (25.0)	1417 (48.2)	67 (46.2)	4679 (41.0)	20,980
Air Force	12,925 (31.9)	2669 (33.0)	664 (22.6)	32 (22.1)	3699 (32.4)	19,989
Navy	11,790 (29.1)	3097 (38.3)	736 (25.0)	43 (29.7)	2474 (21.7)	18,140
Marines	2954 (7.3)	300 (3.7)	124 (4.2)	3 (2.1)	566 (5.0)	3947
Maternal rank						
Enlisted	35,122 (86.8)	7364 (91.0)	2759 (93.8)	133 (91.7)	10,327 (90.4)	55,705
Officer	5338 (13.2)	728 (9.0)	182 (6.2)	12 (8.3)	1091 (9.6)	7351
Maternal occupation						
All others	29,087 (71.9)	6422 (79.4)	2405 (81.8)	111 (76.6)	9155 (80.2)	47,180
Health care	8681 (21.5)	767 (9.5)	219 (7.4)	15 (10.3)	1441 (12.6)	11,123
Combat	2692 (6.7)	903 (11.2)	317 (10.8)	19 (13.1)	822 (7.2)	4753
Maternal duty status						
Regular	34,117 (84.3)	7361 (91.0)	2661 (90.5)	129 (89.0)	10 427 (91.3)	54,695
Reserve/other	6343 (15.7)	731 (9.0)	280 (9.5)	16 (11.0)	991 (8.7)	8361

graphic information. This subset of infants did not differ from the study cohort with regard to the proportion of overall birth defects or preterm birth.

DISCUSSION

Although pregnancy should preclude women from deploying to war, some U.S. service women were inadvertently deployed to the post-2001 wars in Iraq and Afghanistan before their pregnancy was recognized, or they conceived their pregnancies in theater. The current analyses represent the first large-scale epidemiologic investigation of adverse health events among infants born to women who deployed to these operational theaters. Our findings indicate that infants born between 2002 and 2005 to military women who were deployed during early pregnancy were not at increased risk for being born preterm, being diagnosed with a major birth defect, or being diagnosed with a malignancy in the first year of life.

The finding of no increase in preterm births after deployment exposure in early pregnancy may be reassuring to those concerned that the stressors of such exposure would create a high-risk pregnancy (Endara et al., 2009; Magann et al., 1996; McNeary and Lomenick, 2000). Also, although the current study was unable to evaluate pregnancy losses, rates of preterm birth may be an indirect measure of the risk for some etiologies of spontaneous pregnancy loss, since placental challenges may result in either loss or preterm delivery (Norwitz, 2006). Similarly, the sex ratio (male:female) has sometimes been considered an indirect measure of pregnancy losses in a population (Bruckner and Catalano, 2007; Catalano and Bruckner, 2006). Our finding of no decrease in the sex ratio among liveborn infants also supports the assertion that pregnancy losses may not have been higher among the exposed population. Nonetheless, it is important to note that any analyses of a cohort of liveborn infants cannot directly evaluate early or late pregnancy losses.

Table 2
Adjusted* Odds of Preterm and Extreme Preterm Singleton Birth among Infants Born to Women who Deployed to Military Operations, with Alternative Models

Characteristic	Preterm* OR [†] (95% CL) [†]	Extreme preterm* OR [†] (95% CL) [†]
Primary model		
Deployed prepregnancy or postpregnancy (reference)	1.00 (—)	1.00 (—)
Deployed during pregnancy	1.13 (0.97–1.32)	1.11 (0.73–1.68)
Alternative model		
Deployed postpregnancy (reference)	1.00 (—)	1.00 (—)
Deployed during pregnancy	1.14 (0.97–1.34)	1.26 (0.81–1.98)
Alternative model		
Never deployed (reference)	1.00 (—)	1.00 (—)
Deployed during pregnancy	1.05 (0.91–1.22)	0.95 (0.64–1.42)

*Preterm birth was defined as estimated gestational age (EGA) between 28 and 36 weeks; extreme preterm birth was defined as EGA of 28 weeks or earlier. The referent group for the outcome in all models was full-term birth, defined as EGA of at least 36 weeks.

[†]Polychotomous logistic regression models were adjusted for infant gender, maternal age, race/ethnicity, marital status, military service branch, military rank, and military occupation.

OR, odds ratio; 95% CLs, 95% confidence limits.

As previously noted, birth defects remain important reproductive health outcomes in any population with exposures of concern. The prevalence of birth defects in infants born to military women who inadvertently deployed during early pregnancy was slightly higher than referent populations, but this difference was not statistically significant. The prevalence of hydrocephalus without spina bifida was also higher among infants in the exposed group, although this difference was not statistically significant when adjusted for multiple comparisons. Nonetheless, this finding is interesting in light of hypotheses about emerging infectious diseases that may be more common in some parts of the world, and their relationship to congenital malformations (Niklasson et al., 2009). These findings underscore the importance of additional analyses based on specific maternal exposures, whenever possible.

A notable strength of this study was the ability to evaluate birth defects and other infant health outcomes objectively through the entire first year of life. This allowed for the assessment of some outcomes that are not always considered in the reproductive health spectrum, but that could be related to parental or fetal exposures. Neoplasms of infancy seem to have common developmental pathways with some birth defects and deserve closer consideration as reproductive health outcomes (Bukowinski et al., 2008). Malignant neoplasms in the first year of life are especially concerning and, although some links to prenatal exposures have been suggested (Feychting et al., 2001; Ross and Swensen, 2000; Wigle et al., 2008), the causes of most infant cancer cases remain unknown. Our analyses were not able to evaluate the association

Table 3
Adjusted* Odds of Birth Defects among Infants Born to Women who Deployed to Military Operations

Variable		Total infants	Infants with birth defects n (%)	OR* (95% CL)*
Deployment timing [†]	Outside 1st trimester	19,655	667 (3.39)	
	Within 1st trimester	2941	113 (3.84)	1.14 (0.93–1.40)
Infant plurality	Singleton	22,362	762 (3.41)	
	Multiple	234	18 (7.69)	2.27 (1.33–3.85)
Infant gender	Female	10,933	300 (2.74)	
	Male	11,663	480 (4.12)	1.52 (1.31–1.75)
Maternal age at birth	<35 years	21,455	725 (3.38)	
	≥35 years	1141	55 (4.82)	1.45 (1.09–1.94)
Maternal race/ethnicity	White	9680	330 (3.41)	
	Black	8044	290 (3.61)	1.08 (0.91–1.28)
	Hispanic	2861	105 (3.67)	1.12 (0.89–1.40)
	Asian/other/unknown	2011	55 (2.73)	0.82 (0.61–1.09)
Maternal marital status	Married	14,531	491 (3.38)	
	Unmarried	8065	289 (3.58)	1.06 (0.91–1.24)
Maternal service branch	Army	8189	257 (3.14)	
	Air Force	7064	246 (3.48)	1.17 (0.97–1.42)
	Navy	6350	246 (3.87)	1.32 (1.10–1.58)
	Marines	993	31 (3.12)	1.09 (0.75–1.60)
Maternal military rank	Enlisted	20,583	706 (3.43)	
	Officer	2013	74 (3.68)	0.72 (0.49–1.04)
Maternal occupation	All others	18,093	624 (3.45)	
	Health care	2442	90 (3.69)	1.06 (0.84–1.34)
	Combat	2061	66 (3.20)	0.87 (0.67–1.13)
Maternal duty status	Regular	20 578	689 (3.35)	
	Reserve/other	2018	91 (4.51)	1.71 (1.23, 2.37)

*Multivariable logistic regression adjusted for all variables shown.

[†]Deployed outside 1st trimester includes all infants born to women who deployed in prepregnancy, late pregnancy, or postpregnancy periods.

OR, odds ratio; 95% CLs, 95% confidence limits.

Table 4
Comparison of Primary and Alternative Models: Adjusted* Odds of Birth Defects among Infants Born to Military Women, by Maternal Deployment Experience

	Referent group for maternal deployment					
	Deployed outside of 1st trimester (primary model)	Deployed postpregnancy		Never deployed		
Exposure groups with associated ORs and 95% CLs	1st trimester deployed	1.14 (0.93–1.40)	1st trimester deployed	1.13 (0.91–1.41)	1st trimester deployed	1.06 (0.87–1.29)
			Prepregnancy deployed	1.03 (0.88–1.21)	Prepregnancy deployed	0.97 (0.85–1.10)
			Late-pregnancy deployed	0.82 (0.22–2.20) [†]	Late-pregnancy deployed	0.75 (0.20–1.99) [‡]
					Postpregnancy deployed	0.92 (0.82–1.04)
					Ever-deployed	0.96 (0.88–1.05)

*Models adjusted for infant plurality, infant gender, maternal age at birth, race/ethnicity, marital status, military service branch, military rank, military occupation, and duty status, when available. Odds ratios with 95% confidence limits shown.

[†]Exact logistic regression model adjusted for infant plurality and infant gender.

[‡]Exact logistic regression model adjusted for infant gender and maternal race/ethnicity.

ORs, odds ratios; 95% CLs, 95% confidence limits.

between maternal deployment in early pregnancy and infant malignancies due to the small number of cases.

This study has several additional limitations that must be considered in interpretation of results. First, military deployment is a broad measure of exposure and conclusions based on this analysis should be made with the understanding of the complexity and heterogeneity of exposures during deployment. Specific deployment locations and exposure levels of potential hazards were not available for these analyses. Although military women are promptly moved out of the operational theater after a pregnancy is recognized, the duration of exposure to any deployment-related hazards cannot be fully assessed. Other limitations are related to reliance on electronic databases for both maternal and infant information, such that misclassification bias may have occurred when identifying the timing of pregnancy or deployment. Data challenges precluded the capture of all multiple births in the cohort. Not all maternal exposure variables, including tobacco, alcohol, and medication use, could be included in multivariable models. It is possible that some of the maternal

demographic factors associated with adverse outcomes, such as enlisted rank and Reserve status, actually reflect differences in smoking and alcohol use that have been observed in other military studies (Jacobson et al., 2008b; Smith et al., 2008). Infant medical diagnoses from electronic databases include some degree of miscoding. Similarly, definitions of EGA based on coding of birth records are likely to introduce some degree of error. It may be assumed, however, that errors introduced by miscoding in infant and birth records are nondifferential with regard to maternal deployment experience. Validation of electronic diagnostic coding by clinical record review additionally mitigated the effects of these challenges.

Finally, any analysis restricted to live births cannot capture pregnancy losses as a critical reproductive health outcome, nor congenital anomalies within such losses. Although many birth defects surveillance systems are still based on cohorts of live births, some evaluations have shown that prenatally identified defects in electively terminated pregnancies may represent a substantial pro-

Table 5
Adjusted* Odds of Selected Birth Defects among Infants Born to Women who Deployed to Military Operations

Defect category	ICD-9-CM codes	Deployed within 1st trimester n (%) of 2941 infants	Deployed outside of 1st trimester n (%) of 19,655 infants	OR* (95% CL)*
Patent ductus arteriosus [†]	747.0	13 (0.44)	117 (0.60)	0.77 (0.34–1.75)
Ventricular septal defect	745.4	20 (0.68)	103 (0.52)	1.36 (0.69–2.69)
Atrial septal defect [†]	745.5	16 (0.54)	103 (0.52)	1.04 (0.49–2.23)
Hypospadias or epispadias [‡]	752.61, 752.62	16 (1.04)	91 (0.90)	1.16 (0.54–2.48)
Obstructive genitourinary defects	753.2, 753.6	12 (0.41)	66 (0.34)	1.19 (0.48–2.92)
Pulmonary valve atresia or stenosis	746.01, 746.02	11 (0.37)	46 (0.23)	1.56 (0.62–3.95)
Pyloric stenosis	537.0, 750.5	7 (0.24)	47 (0.24)	0.90 (0.29–2.83)
Congenital hip dislocation	754.3	8 (0.27)	29 (0.15)	2.11 (0.65–6.85)
Hydrocephalus without spina bifida	742.3 w/o 741.0, 741.9	7 (0.24)	16 (0.08)	3.16 (0.94–10.63)

*Models adjusted for infant plurality, infant gender, maternal age at birth, race/ethnicity, marital status, military service branch, military rank, military occupation, and duty status, when available; outcomes were included in modeling if at least 5 cases were identified in each exposure group.

[†]Excludes diagnoses in preterm infants.

[‡]Analysis restricted to male infants.

ICD-9-CM, International Classification of Diseases; OR, odds ratio; 95% CLs, 95% confidence limits with Bonferroni adjustment, w/o, without.

portion of all pregnancies affected by congenital anomalies (Cragan and Gilboa, 2009; Forrester et al., 1998; Siffel et al., 2004). It is unclear how inclusion of electively terminated pregnancies might have affected results of these analyses, if inclusion of such data were possible. Because maternal military deployment during pregnancy is not intended, prenatal care might be delayed more often in such pregnancies, possibly limiting options for elective termination. If so, higher rates of birth defects might be expected in the cohort of infants with maternal deployment during pregnancy; however, no statistically significantly higher rates were observed in infants born to exposed women in these analyses.

Important strengths of this study include its large cohort size and ability to capture relatively complete objective measures of all demographic variables, military deployment dates, and outcome measures. The large sample size allowed for an appropriate referent population to be defined as infants born to military women who deployed outside of the first trimester of pregnancy. This referent group was considered optimal because deployable woman may differ in important ways from never-deployed military women (Lindstrom et al., 2006). Alternative models explored other potential relationships between deployment timing and reproductive health outcomes. The consistency of results in alternative models supports the overall conclusions of this study.

Findings of this study are consistent with findings from other recent evaluations of inadvertent deployment-related exposures to military women during pregnancy (Ryan et al., 2008a; Ryan et al., 2008b; Ryan and Seward, 2008). Although results have been reassuring to date, it remains important to evaluate specific military occupational exposures, separately and in combination, and their potential effects on reproductive health. Although military policy will continue to attempt to prevent exposures to potential hazards in pregnancy, any young, healthy population of service women is likely to have some inadvertent exposures when pregnancies are unplanned or mistimed (Chung-Park, 2007; Thomas et al., 2001). It is important to evaluate the outcomes of such pregnancies, particularly when exposures can be defined as within a vulnerable period of fetal development. Studies of military occupational exposures represent valuable contributions to our growing understanding of the ways environmental factors affect health, from the prenatal period through childhood and beyond (Landrigan et al., 2006; Smith, 2009).

In summary, this exploratory study was the first to investigate adverse health outcomes among infants born to U.S. military women who deployed in support of post-2001 military operations. We found no overall associations between maternal deployment in early pregnancy and preterm birth or birth defects in infants. While malignant neoplasms were too few in these analyses to make meaningful conclusions, it may be reassuring that these concerning diagnoses remained rare in both exposed and comparison populations and no clusters were evident. Due to the broad nature of deployment as an exposure, future analyses should attempt to examine outcomes related to specific maternal exposures during deployment, and outcomes among the growing number of infants conceived after deployment.

ACKNOWLEDGMENTS

In addition to the authors, members of the DoD Birth and Infant Health Registry team include Ania Bukowski,

Kathy Snell, and Brian Feldman. The authors thank Scott L. Seggerman and Greg D. Boyd from the United States Defense Manpower Data Center, Monterey Bay, California, for providing demographic and deployment data, and Michelle Stoia, from the Naval Health Research Center, San Diego, California, for editorial assistance. The authors appreciate the support of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland.

REFERENCES

- Alvord V. 2003. January 26, 2003. Some troops freeze sperm before deploying. *USA Today*.
- Araneta MR, Kamens DR, Zau AC, et al. 2004. Conception and pregnancy during the Persian Gulf War: the risk to women veterans. *Ann Epidemiol* 14:109–116.
- Arfsten DP, Still KR, Ritchie GD. 2001. A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development. *Toxicol Ind Health* 17:180–191.
- Aschengrau A, Monson RR. 1990. Paternal military service in Vietnam and the risk of late adverse pregnancy outcomes. *Am J Public Health* 80:1218–1224.
- Briggs J. 1995. The tiny victims of Desert Storm. Has our country abandoned them? *Life Magazine* 46–61.
- Bruckner T, Catalano R. 2007. The sex ratio and age-specific male mortality: evidence for culling in utero. *Am J Hum Biol* 19:763–773.
- Bukowski AT, Ryan MA, Slymen DJ, et al. 2008. Haemangiomas and associated congenital malformations in a large population-based sample of infants. *Paediatr Perinat Epidemiol* 22:520–529.
- Catalano R, Bruckner T. 2006. Secondary sex ratios and male lifespan: damaged or culled cohorts. *Proc Natl Acad Sci U S A* 103:1639–1643.
- Chung-Park MS. 2007. Contraceptive decision-making in military women. *Nurs Sci Q* 20:281–287.
- Correa-Villaseñor A, Cragan J, Kucik J, et al. 2003. The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention. *Birth Defects Res A Clin Mol Teratol* 67:617–624.
- Cowan DN, DeFraitte RF, Gray GC, et al. 1997. The risk of birth defects among children of Persian Gulf War veterans. *N Engl J Med* 336:1650–1656.
- Cragan JD, Gilboa SM. 2009. Including prenatal diagnoses in birth defects monitoring: experience of the Metropolitan Atlanta Congenital Defects Program. *Birth Defects Res A Clin Mol Teratol* 85:20–29.
- Doyle P, Maconochie N, Davies G, et al. 2004. Miscarriage, stillbirth and congenital malformation in the offspring of UK veterans of the first Gulf war. *Int J Epidemiol* 33:74–86.
- Doyle P, Maconochie N, Ryan M. 2006. Reproductive health of Gulf War veterans. *Philos Trans R Soc Lond B Biol Sci* 361:571–584.
- Endara SM, Ryan MA, Sevcik CJ, et al. 2009. Does acute maternal stress in pregnancy affect infant health outcomes? Examination of a large cohort of infants born after the terrorist attacks of September 11, 2001. *BMC Public Health* 9:252.
- Feychting M, Plato N, Nise G, Ahlbom A. 2001. Paternal occupational exposures and childhood cancer. *Environ Health Perspect* 109:193–196.
- Forrester MB, Merz RD, Yoon PW. 1998. Impact of prenatal diagnosis and elective termination on the prevalence of selected birth defects in Hawaii. *Am J Epidemiol* 148:1206–1211.
- Hanke W, Jurewicz J. 2004. The risk of adverse reproductive and developmental disorders due to occupational pesticide exposure: an overview of current epidemiological evidence. *Int J Occup Med Environ Health* 17:223–243.
- Jacobson IG, Gumbus GR, Sevcik CJ, et al. 2008a. Smallpox vaccination is not associated with infertility in a healthy young adult population. *Hum Vaccin* 4.
- Jacobson IG, Ryan MA, Hooper TI, et al. 2008b. Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA* 300:663–675.
- Kang HK, Mahan CM, Lee KY, et al. 2000. Pregnancy outcomes among U.S. women Vietnam veterans. *Am J Ind Med* 38:447–454.
- Kang H, Magee C, Mahan C, et al. 2001. Pregnancy outcomes among U.S. Gulf War veterans: a population-based survey of 30,000 veterans. *Ann Epidemiol* 11:504–511.
- Kelly JF. 2003. Deploying soldiers put family plans on ice. *Washington Post B1, B2*.
- Landrigan PJ, Trasande L, Thorpe LE, et al. 2006. The National Children's Study: a 21-year prospective study of 100,000 American children. *Pediatrics* 118:2173–2186.

- Liang K-Y, Zeger SL. 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73:13–22.
- Lindstrom KE, Smith TC, Wells TS, et al. 2006. The mental health of U.S. military women in combat support occupations. *J Womens Health (Larchmt)* 15:162–172.
- Magann EF, Winchester MJ, Carter DP, et al. 1996. Military pregnancies and adverse perinatal outcome. *Int J Gynaecol Obstet* 52:19–24.
- McNeary AM, Lomenick TS. 2000. Military duty: risk factor for preterm labor? A review. *Mil Med* 165:612–615.
- Ngo AD, Taylor R, Roberts CL, Nguyen TV. 2006. Association between Agent Orange and birth defects: systematic review and meta-analysis. *Int J Epidemiol* 35:1220–1230.
- Niklasson B, Samsioe A, Papadogiannakis N, et al. 2009. Zoonotic Ljungan virus associated with central nervous system malformations in terminated pregnancy. *Birth Defects Res A Clin Mol Teratol* 85:542–545.
- Norwitz ER. 2006. Defective implantation and placentation: laying the blueprint for pregnancy complications. *Reprod Biomed Online* 13:591–599.
- Reutman SR, LeMasters GK, Knecht EA, et al. 2002. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. *Environ Health Perspect* 110:805–811.
- Ross JA, Swensen AR. 2000. Prenatal epidemiology of pediatric tumors. *Curr Oncol Rep* 2:234–241.
- Ryan MA, Gumbs GR, Conlin AM, et al. 2008a. Evaluation of preterm births and birth defects in liveborn infants of US military women who received smallpox vaccine. *Birth Defects Res A Clin Mol Teratol* 82:533–539.
- Ryan MA, Pershyn-Kisor MA, Honner WK, et al. 2001. The Department of Defense Birth Defects Registry: overview of a new surveillance system. *Teratology* 64 Suppl 1:S26–29.
- Ryan MA, Seward JF; Smallpox Vaccine in Pregnancy Registry Team. 2008. Pregnancy, birth, and infant health outcomes from the National Smallpox Vaccine in Pregnancy Registry, 2003–2006. *Clin Infect Dis* 46 Suppl 3:S221–226.
- Ryan MA, Smith TC, Seveck CJ, et al. 2008b. Birth defects among infants born to women who received anthrax vaccine in pregnancy. *Am J Epidemiol* 168:434–442.
- Sever L. 2004. National Birth Defects Prevention Network (NBDPN). Guidelines for Conducting Birth Defects Surveillance. Atlanta: National Birth Defects Prevention Network, Inc.
- Siffel C, Correa A, Cragan J, Alverson CJ. 2004. Prenatal diagnosis, pregnancy terminations and prevalence of Down syndrome in Atlanta. *Birth Defects Res A Clin Mol Teratol* 70:565–571.
- Smith B, Ryan MA, Wingard D, et al. for the Millennium Cohort Study Team. 2008. Cigarette smoking and military deployment: a prospective evaluation. *Am J Prev Med* 35:539–546.
- Smith TC; Millennium Cohort Study Team. 2009. The US Department of Defense Millennium Cohort Study: career span and beyond longitudinal follow-up. *J Occup Environ Med* 51:1193–1201.
- Stellman SD, Stellman JM, Sommer JF Jr. 1988. Health and reproductive outcomes among American Legionnaires in relation to combat and herbicide exposure in Vietnam. *Environ Res* 47:150–174.
- Thomas AG, Brodine SK, Shaffer R, et al. 2001. Chlamydial infection and unplanned pregnancy in women with ready access to health care. *Obstet Gynecol* 98:1117–1123.
- Wells TS, Wang LZ, Spooner CN, et al. 2006. Self-reported reproductive outcomes among male and female 1991 Gulf War era US military veterans. *Matern Child Health J* 10:501–510.
- Wheeler W, Kroemer K, Coperland R, et al. 1994. Operation Desert Storm. Questions remain on possible exposure to reproductive toxicants. Washington, DC: Government Accountability Office.
- Wigle DT, Arbuckle TE, Turner MC, et al. 2008. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev* 11:373–517.

REPORT DOCUMENTATION PAGE

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1. REPORT DATE (DD MM YY) 23 03 09		2. REPORT TYPE Journal submission		3. DATES COVERED (from – to) 2002 to 2005	
4. TITLE AND SUBTITLE Health Outcomes among Infants Born to Women Deployed to US Military Operations during Pregnancy				5a. Contract Number:	
6. AUTHORS Margaret A.K. Ryan, MD, MPH; Isabel G. Jacobson, MPH; Carter J. Sevick, MS; Tyler C. Smith, MS, Ph.D.; Gia R. Gumbs, MPH; Ava Marie S. Conlin, DO, MPH; for the DoD Birth and Infant Health Registry Team				5b. Grant Number:	
				5c. Program Element Number:	
				5d. Project Number:	
				5e. Task Number:	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Commanding Officer Naval Health Research Center 140 Sylvester Rd San Diego, CA 92106-3521				5f. Work Unit Number: 60504	
8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES) Commanding Officer Naval Medical Research Center 503 Robert Grant Ave Silver Spring, MD 20910-7500 Commander Navy Medicine Support Command P.O. Box 140 Jacksonville, FL 32212-0140				8. PERFORMING ORGANIZATION REPORT NUMBER Report No. 09-18	
				10. SPONSOR/MONITOR'S ACRONYM(S) NMRC/NMSC	
				11. SPONSOR/MONITOR'S REPORT NUMBER(s)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Background: Pregnant woman are generally exempt from deployment to military operations. However, exposures to such environments may inadvertently occur in pregnancy. This study examined whether maternal deployment during pregnancy was associated with any adverse health outcome in infants. Results: There were 2941 infants born to women who appeared to have been deployed some time during the first trimester of pregnancy. Compared with infants born to women deployed at other times, or never deployed, "exposed" infants were not more likely to be born preterm, diagnosed with a major birth defect, or diagnosed with a malignancy. Conclusions: Infants born to women who inadvertently deployed to military operations during their pregnancy were not at increased risk of any adverse birth or infant health outcomes.					
15. SUBJECT TERMS congenital abnormalities, premature birth, military personnel, neoplasms					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UNCL	18. NUMBER OF PAGES 8	18a. NAME OF RESPONSIBLE PERSON Commanding Officer
a. REPORT UNCL	b. ABSTRACT UNCL	c. THIS PAGE UNCL			18b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429