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Birth Defects in Infants Born in 1998–2004 to Men and Women Serving in the U.S. Military during the 1990–1991 Gulf War Era

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BACKGROUND: Concerns about reproductive health persist among U.S. military members who served in the 1990–1991 Gulf War. This study explores the long-term impact of 1990–1991 Gulf War deployment on the prevalence of birth defects among infants of Gulf War veterans. **METHODS:** Health care data from the Department of Defense Birth and Infant Health Registry and demographic and deployment information from the Defense Manpower Data Center were used to identify infants born between 1998 and 2004 to both male and female 1990–1991 Gulf War veterans. Multivariable logistic regression models estimated the adjusted odds of any birth defect and eight specific birth defects among infants of deployers versus non-deployers. In addition, birth defects were evaluated among infants born to 1990–1991 Gulf War veterans with deployment-specific exposures. **RESULTS:** Among 178,766 infants identified for these analyses, 3.4% were diagnosed with a birth defect in the first year of life. Compared to infants of non-deployers, infants of deployers were not at increased odds of being diagnosed with a birth defect, or any of eight specific birth defects, in the first year of life. A slightly increased prevalence of birth defects was observed among infants born to men who deployed to the 1990–1991 Gulf War for 153 to 200 days compared to those who deployed for 1 to 92 days. No other deployment-specific exposures were associated with birth defects in these infants. **CONCLUSIONS:** The 1990–1991 Gulf War deployers, including those with specific exposures of concern, were not found to be at increased risk for having infants with birth defects 7 to 14 years after deployment. *Birth Defects Research (Part A) 94:721–728, 2012.* Published 2012 Wiley Periodicals, Inc.[†]

Key words: Gulf War; birth defects; military; environmental exposures; reproductive health

INTRODUCTION

Public and veteran concern has prompted extensive research into the health of 1990–1991 Gulf War veterans after the war. Of particular concern were adverse reproductive outcomes presumably caused by exposure to potentially hazardous substances encountered during deployment. In 1994, the U.S. General Accounting Office identified 21 possible reproductive toxicants and teratogens that were present during the 1990–1991 Gulf War, which included agents present in smoke from the Kuwaiti oil well fires, soil samples, and pesticides (United States General Accounting Office, August 1994; Warden, 1996; Smith et al., 2002). Most epidemiologic studies of this issue in the 1990s showed inconclusive or negative results (Penman et al., 1996; Cowan et al., 1997; Araneta et al., 2000; Ishøy et al., 2001; Doyle et al., 2004; Werler et al., 2005; Doyle et al., 2006; Wells et al., 2006) although

some have suggested significantly more self-reported ectopic pregnancies and spontaneous abortions in Gulf War veterans conceiving after but not during the war (Ara-

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neta et al., 2004). A higher prevalence of hypospadias/epispadias has been reported among infants conceived post-war by female Gulf War veterans (Araneta et al., 2003). A higher prevalence of birth defects (Kang et al., 2001), as well as of certain specific birth defects, such as Goldenhar syndrome (Araneta et al., 1997), tricuspid valve insufficiency, aortic valve stenosis, and renal agenesis or hypoplasia, has been reported among infants conceived post-war with male Gulf War veterans (Araneta et al., 2003).

Given the inconsistent findings regarding an association between Gulf War deployment and birth defects, and an overall poor understanding of the etiology of most birth defects, particularly with exposures occurring several years before conception, concerns about the potential continuing effects of deployment and related exposures persist among veterans of the Gulf War era. Studies exploring the more recent reproductive health experience of the aging Gulf War-era cohort are limited to self-reported data, and suggest that male Gulf War veterans are not at increased risk for adverse reproductive outcomes associated with deployment to the 1990–1991 Gulf War (Kelsall et al., 2007) or self-reported deployment-specific exposures (Verret et al., 2008). A better understanding of the long-term consequences of specific exposures, such as nerve agents released as a result of munitions demolitions at Khamisiyah, Iraq (Gray et al., 1999; Smith et al., 2003), smoke from Kuwaiti oil well fires (Smith et al., 2002), and in-theater hospitalizations (Smith et al., 2004), is critical to the continued health of military members and their offspring. The Department of Defense (DoD) Birth and Infant Health Registry, established in 1998, was developed to address such issues. The purpose of this analysis was to investigate the long-term reproductive health of both female and male 1990–1991 Gulf War veterans, as measured by the prevalence of birth defects in their infants born 7 to 14 years after the war, incorporating deployment-specific exposure data.

METHODS

Study Population

The DoD Birth and Infant Health Registry (Ryan et al., 2001) identified a total of 181,155 infants born in 1998–2004 to 1990–1991 Gulf War-era veterans (both deployed and non-deployed personnel). This database includes all DoD-sponsored health care, inpatient and outpatient, at both military and civilian facilities, for infants born to military families worldwide. For the present study, only infants in the DoD Birth and Infant Health Registry with at least one parent known to be a 1990–1991 Gulf War-era veteran were included in the study population. Infants of Gulf War-era non-deployed veterans served as the control group. Infants with missing covariate data ($n = 2389$) were excluded, resulting in 178,766 infants for these analyses.

Among those infants whose parent(s) deployed to the 1990–1991 Gulf War, analyses incorporated available deployment-specific exposures, including days in theater (categorized into quartiles), potential exposure to nerve agents at Khamisiyah, potential exposure to smoke from Kuwaiti oil well fires, in-theater hospitalization, and deployment during the major combat period, from January to March 1991.

Birth Defect Outcomes

Birth defects were categorized according to criteria established by the National Birth Defects Prevention Network (NBDPN), 2005), which utilizes standard International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for major congenital anomalies (740.xx–759.xx) as well as fetal alcohol syndrome (760.71). As per Metropolitan Atlanta Congenital Defects Program guidelines when applied to ICD-9-CM coded diagnoses, cases of atrial septal defect (745.5x) and patent ductus arteriosus (747.0x) in preterm infants were not included as birth defects (Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program, 1998; Correa et al., 2007). For these analyses, any birth defect was used as the primary outcome. Additionally, eight specific birth defects were chosen as secondary outcomes for further analyses in this report. These outcomes included the five most prevalent birth defects based on data from the present study population (atrial septal defect, ventricular septal defect, patent ductus arteriosus, hypospadias/epispadias, and congenital hip dislocation), as well as three birth defects previously reported to be significantly associated with deployment to the 1990–1991 Gulf War (aortic valve stenosis, hypoplastic left heart syndrome, and renal agenesis/dysgenesis) (Araneta et al., 2003).

Khamisiyah

The DoD announced on June 21, 1996, that it appeared that U.S. forces had destroyed a bunker and a nearby pit containing chemical weapons and munitions near Khamisiyah, Iraq, on March 10, 1991, possibly exposing service members to hazardous levels of gaseous nerve agents, including sarin and cyclosarin. Hazardous exposure levels were based on an adjusted general population limit, a health standard established by the Centers for Disease Control and Prevention, of 0.000003 mg/m^3 for sarin and 0.00001 mg/m^3 for cyclosarin (Smith et al., 2003). To identify and characterize the risk of individuals exposed to this hazardous area, the DoD and the Central Intelligence Agency reconstructed the demolition at Khamisiyah using computer-modeling techniques to determine the size and path of the potentially hazardous area (Central Intelligence Agency, 2006). The results of these modeling efforts were released in 1997 in the first interim report (Central Intelligence Agency, 2006). Over the next 3 years, further refinement of these computer-modeling techniques was completed with the aid of the following: an updated Central Intelligence Agency estimate of the amount of chemical warfare agent released, the addition of information to the models regarding deposition and decay, and consideration of the toxicity of both sarin and cyclosarin in the models (Winkenwerder, 2002). Using these revised 2000 Khamisiyah gaseous hazard area modeling data, with exposure estimates for each hazard area and troop location data for specific days in-theater, each Gulf War veteran was classified as possibly exposed or unexposed to hazardous levels of chemical munitions at Khamisiyah (Smith et al., 2003). Further details of this exposure classification can be found elsewhere (Smith et al., 2004).

Oil Well Fire Data

In February 1991, Iraqi troops withdrawing from Kuwait set fire to over half of Kuwait's approximately 1000 oil wells. These fires burned until November 6, 1991, releasing a myriad of environmental contaminants. In response to concerns over exposure to these fires, the U.S. Army Center for Health Promotion and Preventive Medicine (now the U.S. Army Public Health Command), in collaboration with the Air Resources Laboratory of the National Oceanic and Atmospheric Administration, modeled daily particulate matter exposure values using the HYSPLIT model (Draxler and Hess, 1997). These modeled data contained estimates of daily particulate matter concentrations, which were then used to calculate possible troop unit exposure to the oil well fire smoke as troops moved within the 1990–1991 Gulf War theater of operations (Smith et al., 2002). A more detailed description of these data can be found elsewhere (Smith et al., 2003).

Using troop unit exposure estimates in conjunction with the Defense Manpower Data Center (DMDC) Desert Shield/Desert Storm personnel file, with dates of deployment and troop location data for specific days in theater (provided by the U.S. Armed Services Center for Unit Records Research), levels of particulate matter exposure were estimated at the unit level for each Gulf War veteran (Smith et al., 2002). These exposure estimates were then categorized into three levels based on the United States Environmental Protection Agency's National Ambient Air Quality Standards for total suspended particulate exposure (Heller, 2009): no known exposure, low to moderate exposure (average daily exposure of 1–260 $\mu\text{g}/\text{m}^3$ for >1 day or >260 $\mu\text{g}/\text{m}^3$ for 1–25 days), and heavy exposure (average daily exposure of >260 $\mu\text{g}/\text{m}^3$ for >25 days).

Gulf War Hospitalization Data

Gulf War in-theater hospitalization was assessed as a broad measure of overall morbidity that could potentially impact future reproductive health. Hospitalization data were obtained from a database containing archived 1990–1991 Gulf War inpatient hospital records stored at the National Personnel Records Center in St. Louis, Missouri. This database captures information from medical records of Gulf War veterans who were hospitalized in-theater or in Europe (primarily in Germany) from August 1990 through August 1991 (Smith et al., 2004). This work was determined by deployment health specialists and medical record abstractors to contain sufficient information to conduct research on the inpatient hospitalization experience of 1990–1991 Gulf War veterans (Smith et al., 2004).

Abstracted hospitalization data were reviewed twice in their entirety and subjected to a series of quality assurance steps to achieve the greatest possible accuracy (Smith et al., 2004). The information contained in this database included admission date, patient identification, record identification, and associated medical discharge diagnoses coded according to the ICD-9-CM. Any record of an in-theater hospitalization either within the Kuwaiti theater of operations or at a DoD treatment facility in Europe was considered a hospitalization while in-theater (Smith et al., 2004).

Demographic and Service-related Covariates

Demographic and military personnel data were provided by the DMDC and reflected military status as of

the 1990–1991 Gulf War. These data included demographic information on military service members, including gender, birth date, race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, and other), pay grade (enlisted and officer), service branch (Army, Navy, Air Force, and Marine Corps), and duty occupation(s) (non-combat specialist and combat specialist). Race/ethnicity was included in these analyses to adjust for possible racial/ethnic disparities in birth defects (Canfield et al., 2006).

Additional details about births were obtained from the DoD Birth and Infant Health Registry, including infant gender, gestational age, and age of mother at infant's birth (for non-military wives of military men). Birth dates received from the DMDC were used to calculate maternal and paternal age at the time of the infant's birth. Maternal and paternal age were categorized as <35 years and ≥ 35 years. Analyses of infants born to military women did not include paternal age because this information is not documented at the time of birth.

Statistical Analysis

Due to the different mechanisms of teratogenesis between maternal and paternal exposures, analyses were stratified by gender of the Gulf War-era parent. For infants whose parents were both Gulf War-era veterans, inclusion in the paternal or maternal exposure models was based on the following criteria: if the infant's mother was a Gulf War-deployed veteran, then the infant was included in only the maternal exposure models; if the infant's father was a Gulf War-deployed veteran and his or her mother was a non-deployed veteran, then the infant was included in only the paternal exposure models; if both parents were non-deployed veterans, the infant was included in both maternal and paternal models. Of the 178,766 infants in the final analysis data set, 19,320 infants were only in the maternal models, 152,149 infants were only in the paternal models, and 7297 infants were in both.

Descriptive analyses by Gulf War deployment status were completed for both maternal and paternal exposure models. Univariable analyses using chi-square tests of association investigated the significance of unadjusted associations between the exposures of interest and any birth defect. An exploratory regression analysis was conducted to examine regression diagnostics, significant associations, and possible confounding, while simultaneously adjusting for all other variables. The effect of siblings in the data was found to have a negligible impact on results of analyses. Regardless, where possible, generalized estimating equations (Wei et al., 1989) were used to estimate the adjusted odds for the outcomes of interest while adjusting for potentially correlated outcomes among siblings. All analyses were adjusted for demographic and service-related characteristics, as noted in each of the tables for these analyses. Adjusted odds ratios (ORs) of an infant having any birth defect and any of the eight specific birth defects were estimated for deployed versus non-deployed Gulf War-era parents. Adjusted ORs of an infant having any birth defect were also estimated for each of the five specific Gulf War exposures among deployed Gulf War veteran parents. Exact logistic regression was used when cell sizes for any of the exposures of interest were smaller than five (Hirji et al., 1987). If a model was too complex for exact logistic regression,

Table 1
Adjusted ORs for Any Birth Defect among Infants Born in 1998–2004 to Gulf War-era Military Women and Men

Characteristic	Infants born to Gulf War-era women					Infants born to Gulf War-era men				
	Total infants N = 26,617		Infants with birth defects n = 917		OR ^a (95% CI)	Total infants N = 159,446		Infants with birth defects n = 5498		OR ^a (95% CI)
	N	(%)	n	(%)		N	(%)	n	(%)	
Gulf War status										
Non-deployed	23,068	(86.7)	791	(86.3)	1.00	120,132	(75.3)	4162	(75.7)	1.00
Deployed	3549	(13.3)	126	(13.7)	1.05 (0.86–1.28)	39,314	(24.7)	1336	(24.3)	0.98 (0.92–1.05)
Infant's gender										
Female	13,096	(49.2)	401	(43.7)	1.00	77,275	(48.5)	2288	(41.6)	1.00
Male	13,521	(50.8)	516	(56.3)	1.23 (1.08–1.41)	82,171	(51.5)	3210	(58.4)	1.32 (1.25–1.39)
Preterm birth										
Full-term	24,542	(92.2)	751	(81.9)	1.00	147,889	(92.8)	4498	(81.8)	1.00
Preterm	2075	(7.8)	166	(18.1)	2.68 (2.25–3.20)	11,557	(7.3)	1000	(18.2)	2.98 (2.77–3.20)
Paternal age										
<35 years						89,266	(56.0)	2939	(53.5)	1.00
≥35 years						70,180	(44.0)	2559	(46.5)	1.05 (0.99–1.12)
Maternal age										
<35 years	17,822	(67.0)	553	(60.3)	1.00	121,221	(76.0)	3993	(72.6)	1.00
≥35 years	8795	(33.0)	364	(39.7)	1.31 (1.13–1.50)	38,225	(24.0)	1505	(27.4)	1.16 (1.08–1.24)
Race/ethnicity										
White non-Hispanic	15,696	(59.0)	551	(60.1)	1.00	114,089	(71.6)	4023	(73.2)	1.00
Black non-Hispanic	7761	(29.2)	286	(31.2)	1.03 (0.88–1.20)	24,122	(15.1)	794	(14.4)	0.88 (0.81–0.96)
Hispanic	1094	(4.1)	19	(2.1)	0.48 (0.30–0.77)	7765	(4.9)	209	(3.8)	0.74 (0.64–0.85)
Other	2066	(7.8)	61	(6.7)	0.84 (0.64–1.10)	13,470	(8.5)	472	(8.6)	0.98 (0.89–1.09)
Branch of service										
Army	9998	(37.6)	334	(36.4)	1.00	54,025	(33.9)	1829	(33.3)	1.00
Navy	6602	(24.8)	244	(26.6)	1.12 (0.94–1.33)	47,842	(30.0)	1691	(30.8)	1.03 (0.96–1.11)
Marine Corps	946	(3.6)	29	(3.2)	0.95 (0.64–1.40)	15,459	(9.7)	528	(9.6)	1.00 (0.91–1.11)
Air Force	9071	(34.1)	310	(33.8)	1.03 (0.87–1.22)	42,120	(26.4)	1450	(26.4)	1.00 (0.93–1.07)
Pay grade										
Enlisted	21,812	(82.0)	745	(81.2)	1.00	128,655	(80.7)	4447	(80.9)	1.00
Officer	4805	(18.1)	172	(18.8)	0.98 (0.81–1.17)	30,791	(19.3)	1051	(19.1)	0.95 (0.88–1.02)
Occupational category										
Non-combat specialists	24,863	(93.4)	851	(92.8)	1.00	118,331	(74.2)	4119	(74.9)	1.00
Combat specialists	1754	(6.6)	66	(7.2)	1.08 (0.83–1.42)	41,115	(25.8)	1379	(25.1)	0.97 (0.90–1.03)

^aORs adjusted for all variables shown in the table.
OR, odds ratio; CI, confidence interval.

the model was reduced by removing non-confounding covariates until the exact logistic regression could successfully execute. The specific exposures model for infants born to Gulf War deployed women, however, was too complex for exact logistic regression despite model reduction; therefore, for this model, results using generalized estimating equations are presented. It is worth noting, however, that a univariate subanalysis of this variable using exact methods produced results nearly identical to those produced using generalized estimating equations. Dichotomous variables with cell sizes of zero were excluded from models. Finally, because generalized estimating equations cannot be used when any covariate has a cell size of zero, results from standard logistic regression modeling are presented for these situations. Adjusted ORs and 95% confidence intervals (CIs) were calculated for all analyses. Analyses were completed using SAS software (version 9.1.3, SAS Institute, Cary, NC).

RESULTS

A majority of the infants (n = 159,446) were born to Gulf War-era men; 3.4% were diagnosed with a birth defect in their first year of life. Of the 26,617 infants born

to female Gulf War-era personnel, 3.4% were diagnosed with a birth defect in their first year of life. Descriptive statistics are shown in Table 1. Considerably more births were identified for non-deployed Gulf War-era veterans (women and men) than deployed Gulf War veterans. Most infants of Gulf War-era veterans were full-term and were born to mothers or fathers who were white non-Hispanic, under the age of 35 years, and, during the 1990–1991 Gulf War, served in the Army, were of enlisted rank, and were employed in a non-combat occupation (Table 1).

Table 1 also presents adjusted ORs for any birth defect based on select demographic and military characteristics. No association was found between Gulf War deployment status and any birth defect in infants born to Gulf War-era women or men. Infant gender and preterm birth were associated with any birth defect in all models. Male infants were more likely to be diagnosed with a birth defect, as were infants who were born preterm. For both the maternal and paternal exposure models, infants born to mothers older than age 35 years were more likely to have a birth defect. Father's age was not significantly associated with an infant having any birth defect. Hispanic descent was significantly associated with a reduced odds of birth

Table 2
Adjusted ORs for Selected Birth Defects among Infants Born in 1998–2004 to Deployed versus Non-deployed Gulf War-era Military Women and Men

Characteristic	Infants born to Gulf War-era women					Infants born to Gulf War-era men				
	Deployed women n = 3549		Non-deployed women n = 23,068		OR ^b (95% CI)	Deployed men n = 39,314		Non-deployed men n = 120,132		OR ^c (95% CI)
	n	(Prevalence ^a)	n	(Prevalence ^a)		n	(Prevalence ^a)	n	(Prevalence ^a)	
Ventricular septal defect	23	(64.8)	168	(72.8)	0.94 (0.60–1.46)	253	(64.4)	843	(70.2)	0.91 (0.79–1.05)
Atrial septal defect ^d	20	(56.4)	115	(49.9)	1.07 (0.66–1.73)	207	(52.7)	619	(51.5)	1.03 (0.87–1.22)
Aortic valve stenosis ^e	2	(5.6)	5	(2.2)	2.88 (0.26–19.17)	10	(2.5)	36	(3.0)	0.79 (0.39–1.62)
Hypoplastic left heart syndrome ^e	4	(11.3)	8	(3.5)	3.88 (0.80–15.51)	16	(4.1)	49	(4.1)	0.95 (0.54–1.65)
Patent ductus arteriosus ^d	17	(47.9)	121	(52.5)	0.81 (0.49–1.34)	227	(57.7)	647	(53.9)	1.04 (0.89–1.22)
Renal agenesis/dysgenesis ^f	1	(2.8)	14	(6.1)	0.52 (0.01–3.49)	14	(3.6)	38	(3.2)	1.13 (0.60–2.10)
Hypospadias and epispadias ^g	17	(95.6)	117	(99.6)	1.04 (0.61–1.77)	185	(91.4)	561	(90.6)	1.03 (0.86–1.22)
Congenital hip dislocation	11	(31.0)	56	(24.3)	1.55 (0.79–3.04)	95	(24.2)	327	(27.2)	0.92 (0.73–1.17)

^aPrevalence of birth defects per 10,000 liveborn infants.

^bMaternal models adjusted for infant gender, preterm birth, maternal age, race/ethnicity, branch of service, pay grade, and occupation, unless otherwise noted.

^cPaternal models adjusted for infant gender, preterm birth, maternal and paternal age, race/ethnicity, branch of service, pay grade, and occupation, unless otherwise noted.

^dPreterm birth excluded from analyses of atrial septal defect and patent ductus arteriosus for both maternal and paternal models.

^ePay grade and occupation excluded from analyses of aortic valve stenosis and hypoplastic left heart syndrome for maternal models only.

^fBranch of service excluded from analyses of renal agenesis/dysgenesis for maternal model only.

^gAnalyses of hypospadias and epispadias restricted to male infants for both maternal and paternal models.

OR, odds ratio; CI, confidence interval.

defects in both the maternal model and the paternal model, whereas black non-Hispanic descent was associated with a reduced odds of birth defects in only the paternal model.

Analysis results for eight selected birth defects are presented in Table 2. The five most commonly diagnosed birth defects were ventricular septal defect, atrial septal defect, patent ductus arteriosus, hypospadias/epispadias, and congenital hip dislocation (Table 2). In addition to these five birth defects, we analyzed aortic valve stenosis, hypoplastic left heart syndrome, and renal agenesis/dysgenesis. None of the eight specific birth defects were significantly associated with parental deployment to the 1990–1991 Gulf War.

Results of modeling the effects of specific Gulf War parental exposures on any birth defects in infants born to Gulf War-deployed women and men are presented in Table 3. Paternal deployment length was significantly, although inconsistently, associated with birth defects; compared with infants born to fathers in-theater for 1 to 92 days, infants born to fathers in-theater for 153 to 200 days were more likely to have a birth defect, although this trend did not continue for those paternal deployments of 201 to 485 days. None of the other potential exposures studied (i.e., nerve agents at Khamisiyah, smoke from Kuwaiti oil well fires, in-theater hospitalization, or deployment during the major combat period) were significantly associated with birth defects in either parental exposure model.

DISCUSSION

This study represents the first attempt to assess any long-term impact of deployment-specific exposures on the prevalence of birth defects in infants born to both female and male 1990–1991 Gulf War veterans. At least 21 potential reproductive hazards were confirmed as present during the 1990–1991 Gulf War, including agents present in smoke from the Kuwaiti oil well fires, soil samples, and pesticides (United States General Accounting Office, August 1994; Warden, 1996; Smith et al., 2002). Much of the research to date has reported deployment as the aggregated measure of exposure to these hazards, with the exception of a study by Verret et al. (2008) which found no association between self-reported exposures (sandstorms, smoke from oil well fires, chemical or bacteriologic alerts, vaccinations, medication, and pesticides) and the prevalence of birth defects in the children of male Gulf War veterans. In our study, deployment-specific exposure data and in-theater medical care were linked to birth data to investigate the potential for long-term teratogenicity of specific exposures among both female and male veterans of the 1990–1991 Gulf War. These analyses suggest that none of the exposures investigated—potential exposure to nerve agents at Khamisiyah, potential exposure to smoke from Kuwaiti oil well fires, in-theater health care requiring hospitalization, or deployment during the major combat period—were associated with a higher prevalence of birth defects in this population of infants.

Table 3
Adjusted ORs for Birth Defects among Infants Born in 1998–2004 to Gulf War Deployed Women and Men by
Deployment-related Exposure Characteristics

Characteristic	Infants born to Gulf War-deployed women						Infants born to Gulf War-deployed men					
	Total infants N = 3549		Infants with birth defects n = 126		OR ^a	(95% CI)	Total infants N = 39,314		Infants with birth defects n = 1336		OR ^b	(95% CI)
	N	(%)	n	(%)			N	(%)	n	(%)		
No. of days deployed to theatre												
1–92	922	(26.0)	31	(24.6)	1.00		10,076	(25.6)	327	(24.5)	1.00	
93–152	858	(24.2)	38	(30.2)	1.48	(0.88–2.47)	9618	(24.5)	312	(23.4)	1.06	(0.89–1.27)
153–200	797	(22.5)	22	(17.5)	0.80	(0.43–1.48)	9902	(25.2)	371	(27.8)	1.25	(1.05–1.49)
201–485	972	(27.4)	35	(27.8)	1.13	(0.66–1.93)	9718	(24.7)	326	(24.4)	1.11	(0.93–1.34)
Khamisiyah exposure												
No	2840	(80.0)	106	(84.1)	1.00		34,630	(88.1)	1183	(88.5)	1.00	
Yes	709	(20.0)	20	(15.9)	0.68	(0.40–1.14)	4684	(11.9)	153	(11.5)	0.97	(0.81–1.18)
Kuwaiti oil well fire exposure												
No known exposure	1379	(38.9)	43	(34.1)	1.00		14,770	(37.6)	520	(38.9)	1.00	
Low to moderate exposure	1530	(43.1)	58	(46.0)	1.39	(0.90–2.16)	17,360	(44.2)	580	(43.4)	0.97	(0.84–1.12)
Heavy exposure	640	(18.0)	25	(19.8)	1.48	(0.87–2.52)	7184	(18.3)	236	(17.7)	0.98	(0.82–1.17)
In-theater hospitalization												
No	3391	(95.5)	123	(97.6)	1.00		38,524	(98.0)	1300	(97.3)	1.00	
Yes	158	(4.5)	3	(2.4)	0.48	(0.15–1.51)	790	(2.0)	36	(2.7)	1.32	(0.94–1.87)
Deployment during major combat period (Jan–Mar 91)												
No	420	(11.8)	18	(14.3)	1.00		5987	(15.2)	216	(16.2)	1.00	
Yes	3129	(88.2)	108	(85.7)	0.63	(0.33–1.21)	33,327	(84.8)	1120	(83.8)	0.88	(0.72–1.07)

^aORs for any birth defect among infants born to Gulf War deployed women, adjusted for all variables shown in the table, as well as infant gender, preterm birth, maternal age, race/ethnicity, branch of service, pay grade, and occupation.

^bORs for any birth defect among infants born to Gulf War deployed men, adjusted for all variables shown in table, as well as infant gender, preterm birth, maternal and paternal age, race/ethnicity, branch of service, pay grade, and occupation.

OR, odds ratio; CI, confidence interval.

An increased prevalence of birth defects was observed among infants born to men who deployed to theater for moderately long periods of time (153–200 days compared to 1–92 days). Such an association has not been previously reported, and may cause concern given the lengthy deployments of service members to ongoing operations in the Middle East and elsewhere. However, because this trend did not continue to men deployed for greater lengths of time (201–485 days), as one may expect with a causal relationship, and also was not observed among infants born to women deployers, the observed association may simply be spurious.

We report an increased prevalence of birth defects in male infants, preterm infants, and infants born to older mothers. These associations were found in the infants of both female and male Gulf War-era veterans, and they are consistent with previous reports from non-military populations (Hay and Barbano, 1972; Baird et al., 1991; Rasmussen et al., 2001; Shaw et al., 2003; Reefhuis and Honein, 2004; Cui et al., 2005; Porter et al., 2005). Although advanced paternal age has been linked to a number of abnormal reproductive and genetic outcomes (Reichenberg et al., 2006; Wyrobek et al., 2006) the prevalence of birth defects in the infants born to male Gulf War veterans was not associated with paternal age. Both black non-Hispanic and Hispanic race/ethnicity were associated with a reduced odds of birth defects for infants born to male Gulf War veterans, and Hispanic race/ethnicity was associated with a reduced odds of birth defects for infants born to female Gulf War veter-

ans. Although racial/ethnic variations in birth defects have been reported (Canfield et al., 2006), the reasons for these findings are unclear and the possibility that these findings are spurious should be considered.

The DoD Birth and Infant Health Registry, the most comprehensive registry of birth defects in infants born to military personnel, contains nearly all diagnosed birth defects, because approximately 90 to 95% are diagnosed within the first year of life (Stierman, 1994; Bower et al., 2010). Despite distinct advantages, its use in this study may have resulted in some selection bias. Our study population consisted of 1990–1991 Gulf War-era veterans who were in military service during the time period of interest, 1998–2004, and who also had children during this period. We estimate that at the beginning of the study period, approximately 40 to 45% of Gulf War-era veterans remained in military service, and by the end of the study period, approximately 25 to 30% remained in service. Information regarding reproductive health outcomes of those service members who were no longer in military service during the time of this study is not available. It is quite possible that service members who remained in the military a substantial amount of time after the war and had children were healthier than those who left soon after the war, and those who remained in the military but did not have children. Because of this potential bias, the results of this study should be interpreted with caution. Furthermore, the DoD Birth and Infant Health Registry does not capture data on non-DoD-sponsored births or on infants born to service mem-

bers not on active duty at the time of birth. Finally, the Registry does not capture birth defects diagnosed after the first year of life, nor does it contain information on aborted fetuses and stillbirths, because this information is not easily obtainable from electronic medical record data.

Limitations with the 1990–1991 Gulf War exposure data should also be noted. First, although extensive efforts were made to accurately model potential exposure to Khamisiyah nerve agents and oil well fire smoke, acquiring precise, individual-level exposure data remains challenging and results should be interpreted with caution. Second, in-theater hospitalization data are not a complete assessment of hospitalizations that occurred in-theater during the war. A number of U.S. personnel were treated in host-nation hospitals for which records were unavailable and were, therefore, not included in the National Personnel Records Center database. Furthermore, few data were available regarding other possible teratogens, such as depleted uranium (Arfsten et al., 2001), or known teratogens, such as smoking (Werler et al., 2005), alcohol consumption (Larkby and Day, 1997), and pesticide exposure (Hanke and Jurewicz, 2004).

Although it is reasonable to be concerned about the long-term effects of deployment-related exposures on the reproductive health of veterans, it is difficult to isolate them from other exposures of concern including alcohol/tobacco/medication use and various temporally related environmental exposures, which we did not have available for this study. Because these may be equally important as distant war-time exposures, results should be interpreted with care.

Last, sufficient statistical power is a common methodological problem in epidemiologic studies of rare outcomes, such as birth defects. The sample size for this study was adequate to study the association between Gulf War deployment status and overall birth defects; however, assessment of all birth defects could potentially obscure associations between exposures and specific defects. A small number of specific defects for which there was sufficient power were assessed; however, statistical power was not sufficient for assessing additional, less prevalent defects. Furthermore, although analyses were performed for three defects based on previous literature (aortic valve stenosis, hypoplastic left heart syndrome, and renal agenesis/dysgenesis), it is unlikely that there was sufficient power for assessing these specific outcomes.

Despite limitations, these analyses have a number of strengths and unique attributes. The DoD Birth and Infant Health Registry includes the most comprehensive data available to examine birth defects and other reproductive health outcomes in a large cohort of infants with well described health care utilization and parental exposure characteristics. U.S. military data can uniquely define some parental exposures of concern. To our knowledge, these are the first evaluations of infant health related to potential maternal and paternal exposures to complex combustion agents (from oil well fires) and subacute sarin and cyclosarin levels (from bioweapons in Khamisiyah).

The availability of military occupational exposure data continues to grow and now includes aerosolized respiratory particles and combustion agents from open-air burn pits, which are relevant to service members in the more recent theaters of operation in Iraq and Afghanistan (Weese, 2010; Weese and Abraham, 2009; Conlin et al.,

2012). Military data also include expanding details on parental immunizations and medications, which have been valuable in other analyses of infant health outcomes (Ryan and Seward, 2008; Ryan et al., 2008a; Ryan et al., 2008b). All such parental exposure data may contribute to important hypotheses for future research on infant and child developmental health (Landrigan et al., 2006).

In summary, this report provides further evidence that infants born to veterans who deployed during the 1990–1991 Gulf War do not have an increased risk of birth defects. It should be reassuring to past and current military deployers that the effects of the specific exposures investigated do not appear to linger and negatively affect the health of future children. The DoD Birth and Infant Health Registry, when linked with personnel and exposure data, is a valuable tool for investigating the effects of military occupations and exposures on the reproductive health of women and men.

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