Special Article

THE RISK OF BIRTH DEFECTS AMONG CHILDREN OF PERSIAN GULF WAR VETERANS

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ABSTRACT

Background There has been suspicion that service in the Persian Gulf War affected the health of veterans adversely, and there have been claims of an increased rate of birth defects among the children of those veterans.

Methods We evaluated the routinely collected data on all live births at 135 military hospitals in 1991, 1992, and 1993. The data base included up to eight diagnoses from the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) for each birth hospitalization, plus information on the demographic characteristics and service history of the parents. The records of over 75,000 newborns were evaluated for any birth defect (ICD-9-CM codes 740 to 759, plus neoplasms and hereditary diseases) and for birth defects defined as severe on the basis of the specific diagnoses and the criteria of the Centers for Disease Control and Prevention.

Results During the study period, 33,998 infants were born to Gulf War veterans and 41,463 to nondeployed veterans at military hospitals. The overall risk of any birth defect was 7.45 percent, and the risk of severe birth defects was 1.85 percent. These rates are similar to those reported in civilian populations. In the multivariate analysis, there was no significant association for either men or women between service in the Gulf War and the risk of any birth defect or of severe birth defects in their children.

Conclusions This analysis found no evidence of an increase in the risk of birth defects among the children of Gulf War veterans. (N Engl J Med 1997; 336:1650-6.)

SINCE 1991, some of the over 690,000 U.S. veterans of the Persian Gulf War have conceived children born with birth defects, and these children have been the object of much speculation. There have been allegations that the Gulf War veterans had unusual exposures that affected their reproductive health.[1-3] In addition to birth defects, anecdotal reports have suggested that these veterans may also have increased rates of genitourinary morbidity, infertility, and miscarriage.[1,2,4]

A number of investigations have been conducted[5-7] or are under way (unpublished data). Thus far, no increased risk of birth defects has been found among the children of Gulf War veterans; however, recent investigations have been criticized as inadequate.[8,9] Along with other Department of Defense epidemiologic research,[10] this study was conducted to compare the overall risk of birth defects among the offspring of Gulf War veterans with that among children of nondeployed veterans. Because there was no a priori reason to target any subpopulation of Gulf War veterans, this study was not designed to investigate subgroups or small populations that may have had unique exposures.

METHODS

Data Sources

Military data on administration, demographics, and hospitalization were provided by the Defense Manpower Data Center in Monterey Bay, Calif., which maintains Department of Defense data on personnel, manpower, hospitalization, training, and finances. Gulf War service data were obtained from military records detailing deployment location and hostile-fire pay. Demographic data were obtained from routinely maintained administrative files. A routinely generated data base provided information on military hospitalizations.

Study Populations

Of the 696,562 personnel deployed to the Persian Gulf for at least one day from August 8, 1990, to July 31, 1991, 579,931 were active members of the Army, Navy, Marine Corps, or Air Force and were considered Gulf War veterans eligible for inclusion in this study.[11] Reserve-component members were excluded, since neither they nor their families were eligible for care in military hospitals after the sponsor (the service member through whom family members obtain military benefits) was released from active duty.

A comparison group composed of 700,000 service members who were not deployed to the Persian Gulf region — approximately half of all such personnel — was selected from the total

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population of military personnel. Details of the selection process have been presented previously.[11]

The available data included Social Security number, sex, date of birth, race or ethnicity, marital status, service branch, rank, and selected other information, including the dates of deployment to and return from the Persian Gulf region. Information about the date of birth was available for the spouses of male military personnel. Service members for whom selected demographic or military data (such as sex or date of birth) were missing were excluded from analysis of those variables.

Hospitalization Data

Hospitalization data included up to eight diagnoses coded to five digits by medical-records personnel using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). The data on babies included sex and birth date but not birth weight or gestational age. All records include the Social Security number of the sponsor. Records were requested for children and women with codes indicating live births (V30 to V39 and V27.0 to V27.9, respectively). Births paid for by the military that occurred in civilian facilities were identified and used in the estimates of fertility and total number of live births, but because of reliability issues diagnostic data from these records were not used to measure the risk of birth defects.

Eligible Live Births

For the Gulf War veterans, all the live births that occurred before October 1, 1993, with an estimated date of conception (date of birth minus 266 days) after the return of the veteran from the Persian Gulf region, were included. For the nondeployed veterans, all the live births that occurred before October 1, 1993, with an estimated date of conception after December 31, 1990, were included. Each birth, including each of multiple births (e.g., twins), was treated as an independent event.

Outcomes

The primary outcome assessed for this report was the occurrence of birth defects as noted in the medical file. Two secondary outcomes were also considered: the number of live births (per 1000 population) among members of the original cohorts and the ratio of male to female babies.

Two definitions of "birth defect" were used in this report. The first, a very sensitive definition intended to include "any birth defect," was based on the system developed by the Metropolitan Atlanta Congenital Defects Program,[12] which includes essentially all ICD-9-CM codes related to congenital malformations (740 to 759), as well as conditions such as neoplasms and hereditary diseases.

The second definition, which applied to severe birth defects, was based on specific defects considered by the Centers for Disease Control and Prevention (CDC) to be frequent and severe enough to represent a public health problem[13] (and Edmonds L, CDC: personal communication). The groups of severe birth defects that make up 5 percent or more of the total number of severe birth defects were identified, and the relative risk of each group of defects was determined for Gulf War as compared with nondeployed veterans.

Exposure Data

Since possible exposure among service members stationed in the Persian Gulf region to any specific teratogen is speculative and no individual measure of exposure to any specific agent was available, exposure was defined only as deployment to the Gulf region. Deployment was examined according to three-month increments in the duration of deployment and as a continuous variable based on the number of days of deployment. It is possible that there is some underlying unknown difference in the risk of birth defects between Gulf War and nondeployed veterans that varies with deployment to the Gulf region. In order to control at least partially for the possibility of such a difference, the number of days of deployment was evaluated both with nondeployed veterans included (number of days of deployment equals zero), and with only Gulf War veterans included (minimal number of days of deployment equals one).

The interval from the return from the Persian Gulf area to the date of childbirth was also examined for changes in the risk of birth defects over time, and data from the CDC on civilians were used for comparison.

Statistical Analysis

Analyses were conducted with SAS version 6.08 (SAS Institute, Cary, N.C.) and EpiInfo.[14] The univariate measure of association was the relative risk, with statistical significance ($P<0.05$) ascertained by the use of 95 percent confidence intervals. The association between Gulf War service, individual potential confounding factors, and the risk of birth defects was evaluated with Mantel–Haenszel relative risks. Multiple logistic regression was conducted to measure the odds ratio of birth defects associated with Gulf War service, adjusted for confounding factors.

RESULTS

A total of 543,541 male and 35,164 female Gulf War veterans and 613,762 male and 86,192 female nondeployed veterans were identified on whom complete demographic and military information was available. Among the men, 69.4 percent of the Gulf War veterans and 69.8 percent of the nondeployed veterans remained on active duty as of September 30, 1992; as of September 30, 1993, 55.6 percent and 57.4 percent, respectively, remained on active duty. Among the women, 70.3 percent of the Gulf War veterans remained on active duty as of September 30, 1992, as compared with 68.2 percent of the nondeployed veterans; as of September 30, 1993, 56.8 percent and 56.2 percent remained, respectively. All the differences between the deployed and nondeployed veterans were statistically significant.

Of all the identified births that occurred during the study period, 58 percent of the births to the wives of male Gulf War veterans and 57 percent of those to the wives of male nondeployed veterans occurred in military hospitals, as did essentially all (over 99 percent) of the live births to female service members. There were 30,151 children born in military hospitals to the wives of 29,468 male Gulf War veterans and 32,638 born to the wives of 31,646 nondeployed veterans. Among women service members, there were 3847 live births to 3722 Gulf War veterans and 8825 to 8494 nondeployed veterans. Descriptive statistics on service members and the spouses of male service members who gave birth to live offspring in military medical facilities during the study period are shown in Table 1. Male Gulf War veterans were about one year younger on average than the nondeployed veterans, and their wives were about six months younger at delivery than the wives of nondeployed veterans. Male Gulf War veterans were more likely than the nondeployed veterans to be single, black, in the Army, and of enlisted rank. Female Gulf War veterans were, on average, about seven

TABLE 1. CHARACTERISTICS OF SERVICE MEMBERS WITH INFANTS BORN ALIVE IN MILITARY HOSPITALS.*

CHARACTERISTIC	MEN		WOMEN	
	GULF WAR VETERANS	NONDEPLOYED VETERANS	GULF WAR VETERANS	NONDEPLOYED VETERANS
Total live births	30,151	32,638	3847	8825
	percentage of group			
Age of service member on 1/1/91 (yr)				
≤20	10.8	10.0	20.6	18.7
>20–24	35.9	29.7	40.0	35.1
>24–29	33.4	33.8	27.3	29.0
>29–34	14.7	18.2	10.1	13.3
>34–39	4.3	6.4	1.8	3.6
>39	0.9	1.8	0.1	0.4
Age of mother on date of child's birth (yr)				
≤20	0.6	0.6	0.0	0.0
>20–24	17.0	15.4	14.7	15.5
>24–29	38.6	34.6	46.2	39.4
>29–34	28.0	29.0	25.2	26.0
>34–39	11.8	14.8	10.8	13.6
>39	4.0	5.6	3.1	5.5
Marital status of service member on 9/30/90				
Single	35.4	28.3	58.3	48.3
Married	62.5	69.7	37.4	47.8
Previously married	2.0	2.0	4.2	3.6
Other	0.1	0.1	0.1	0.1
Race or ethnic group of service member				
White	69.4	71.5	46.1	53.2
Black	20.0	18.2	45.4	37.1
Hispanic	5.4	5.2	4.1	5.3
American Indian	0.6	0.4	0.9	0.8
Asian	2.9	2.8	1.8	2.1
Other	1.6	1.8	1.6	1.5
Branch of service of service member				
Army	53.4	49.9	68.1	47.5
Air Force	14.9	15.6	8.9	12.7
Marines	12.3	12.2	5.0	8.1
Navy	19.5	22.2	17.9	31.7
Rank group of service member				
Enlisted	87.1	83.6	91.1	88.4
Officer	13.0	16.4	8.9	11.5

*Because of rounding, not all percentages total 100.

months younger than the nondeployed veterans and about six months younger at childbirth. The female Gulf War veterans were more likely to be single, black, in the Army, and of enlisted rank. For all comparisons, the differences were statistically significant.

Among the men identified in the original population, the rate of live births (either in military or civilian hospitals) was 95.64 per 1000 for deployed veterans and 93.29 per 1000 for nondeployed veterans. Among the women the rate was 109.40 per 1000 for deployed veterans and 102.39 per 1000 for nondeployed veterans. Significantly more births were identified for the Gulf War veterans, both male and female, than for the nondeployed veterans. The male-to-female ratio for the children of male Gulf War veterans was 1.06; for the children of male nondeployed veterans it was 1.05. Among female service members, the ratio was 1.04 for Gulf War veterans and 1.02 for nondeployed veterans. There were no significant differences in sex ratios between the children of the Gulf War veterans and the children of the nondeployed veterans.

The unadjusted risks of any birth defect among the children of male and female service members are shown in Table 2. Among male service members, there was no positive association between Gulf War service and the risk of any birth defect, whereas among female service members there was a statistically significant increase in the risk of birth defects for Gulf War veterans, with a relative risk of 1.12 (95

TABLE 2. UNADJUSTED RISK OF ANY BIRTH DEFECT AMONG CHILDREN OF MALE AND FEMALE SERVICE MEMBERS.

OVERALL RISK	CHILDREN OF GULF WAR VETERANS	CHILDREN OF NONDEPLOYED VETERANS	RELATIVE RISK (95% CI)*
	no. (%) with defects		
Children of active-duty men	2137 (7.09)	2339 (7.17)	0.99 (0.93–1.05)
Children of active-duty women	397 (10.32)	810 (9.18)	1.12 (1.00–1.25)
Overall	2534 (7.45)	3149 (7.59)	0.98 (0.93–1.03)
RISK ACCORDING TO TIME IN THEATER (MO)	**NO. (%) WITH DEFECTS**		
Children of men			
0 (nondeployed)	2339 (7.17)		1.00
≤3	442 (6.78)		0.95 (0.86–1.04)
>3–6	899 (7.23)		1.01 (0.94–1.09)
>6–9	729 (7.09)		0.99 (0.91–1.07)
>9–12	67 (7.29)		1.02 (0.81–1.29)
Chi-square test for linear trend = 0.610, P = 0.43			
Children of women			
0 (nondeployed)	810 (9.18)		1.00
≤3	103 (10.73)		1.17 (0.96–1.42)
>3–6	146 (10.76)		1.17 (0.99–1.38)
>6–9	136 (9.99)		1.09 (0.92–1.29)
>9–12	12 (8.00)		0.87 (0.50–1.51)
Chi-square test for linear trend = 2.157, P = 0.14			

*The reference group is the children of nondeployed veterans. CI denotes confidence interval.

percent confidence interval, 1.00 to 1.25). Table 2 also shows the risk of any birth defect according to the length of time in the Persian Gulf region; for the children of both male and female Gulf War veterans there was no association. There was no linear trend of increasing risk with increasing time spent in the Gulf region.

Several potential confounding factors were evaluated with Mantel–Haenszel relative risks (data not shown). Black and single women were more likely to have been deployed and to have a code of "any birth defect" in their infants. Navy and Army women were more likely than Air Force women to have a code of "any birth defect"; Navy women were less likely and Army women more likely to have been deployed. After adjustment for marital status, race or ethnicity, and branch of service, there were no significant associations between Gulf War service and the risk of birth defects, indicating that the significant univariate association was probably due to confounding by these factors.

Table 3 presents the adjusted odds ratios for any birth defect, with Gulf War service evaluated as a dichotomous variable, according to the length of time in the Persian Gulf region in three-month increments, and according to the length of time in the Gulf re-

TABLE 3. ADJUSTED ODDS RATIOS FOR ANY BIRTH DEFECTS.*

EXPOSURE CATEGORY	MALE GULF WAR VETERANS VS. NONDEPLOYED VETERANS	FEMALE GULF WAR VETERANS VS. NONDEPLOYED VETERANS
	adjusted odds ratio (95% CI)†	
Any Gulf War service	0.97 (0.91–1.03)	1.07 (0.94–1.22)
Months of Gulf War service		
0 (nondeployed)	1.00	1.00
≤3	0.92 (0.83–1.03)	1.17 (0.94–1.46)
>3–6	1.00 (0.92–1.08)	1.09 (0.90–1.32)
>6–9	0.96 (0.88–1.05)	1.00 (0.83–1.22)
>9	0.99 (0.77–1.28)	0.78 (0.43–1.41)
Days in Persian Gulf region‡		
Those with ≥0 days	1.000 (0.999–1.000)	1.000 (0.999–1.001)
Those with ≥1 days	1.000 (0.999–1.000)	0.999 (0.998–1.001)

*All models include the mother's age at delivery, the race or ethnicity of the parent in military service, and the marital status of the parent in service at the time of the Gulf War.

†The reference group is the children of nondeployed veterans. CI denotes confidence interval.

‡Odds ratios are per day in the Persian Gulf region.

TABLE 4. UNADJUSTED RISK OF SEVERE BIRTH DEFECTS AMONG CHILDREN OF MALE AND FEMALE SERVICE MEMBERS.

OVERALL RISK	CHILDREN OF GULF WAR VETERANS	CHILDREN OF NONDEPLOYED VETERANS	RELATIVE RISK (95% CI)*
	no. (%) with defects		
Children of active-duty men	554 (1.84)	583 (1.79)	1.03 (0.92–1.15)
Children of active-duty women	76 (1.98)	189 (2.14)	0.92 (0.71–1.20)
Overall	630 (1.85)	772 (1.86)	1.00 (0.90–1.10)

*CI denotes confidence interval.

gion as a continuous variable. In none of these comparisons was there a significant increase in risk for the children of Gulf War veterans.

There was no significant association between Gulf War service and the risk of severe birth defects for the children of either male or female veterans, as shown in Table 4. None of the increments of time spent in the Persian Gulf region were associated with an increase in risk, and there was no evidence of a linear trend of increasing risk with increasing time in the region (data not shown). When the adjusted odds ratios were calculated, no associations were noted (data not shown).

The most commonly occurring groups of severe defects are shown in Tables 5 and 6. For none of the defect groups, including those not shown, were the risks significantly elevated among male or female Gulf War veterans. No association was found between the interval from the return from the Gulf region to the date of childbirth and the risk of any defect or a severe defect.

When the definitions of birth defects (exclusive of neoplasms and hereditary diseases) used in this study were applied to data on approximately 320,000 live births occurring nationwide in 1992 and reported to the CDC Birth Defect Monitoring Program, the risk of any birth defect was 8.4 percent; the risk of a severe defect was 1.9 percent (Edmonds L, CDC: personal communication).

DISCUSSION

This study was designed to test the hypothesis that children born to Gulf War veterans were at an increased overall risk for birth defects. Our findings do not support this hypothesis, since most of the univariate relative risks and all of the adjusted odds ratios were very close to 1.0. In addition, the risk of defects in this military population approximated that in a civilian population. Although the risk of any birth defect was slightly higher among the children of female Gulf War veterans, this appears to be the result of confounding by race or ethnicity, marital status, and branch of service. The negative findings were consistent for the children of male and female service members and for two definitions of birth defects. Furthermore, there was no association between risk and duration of service in the Persian Gulf, and there was no change in risk associated with the interval between the return from the Gulf region and the date of birth. There was no evidence of reduced fertility in this group and no significant differences in the sex ratios of the babies. The findings of this study provide evidence that there are no detectable differences in the overall risk of several adverse reproductive outcomes between deployed and nondeployed service members. Although the study was not designed to examine specific defects or groups of defects, when the most common severe anomalies were examined, no increased risk was found for the children of Gulf War veterans.

This study had certain limitations and certain strengths. Only children born in military hospitals were included (approximately 68 percent of all the births to active-duty military personnel during the study period). Children born after their fathers or mothers left active duty were excluded, as were children born to the more than 110,000 reserve-component personnel. Since the study was limited to live births, no information regarding defects in aborted fetuses or stillbirths was included. Diagnoses made during subsequent hospitalizations, in outpatient settings, or in nonmilitary hospitals were not identified.

The strengths of the study include the large population, resulting in a high degree of statistical power so that the likelihood that effects due to random error were overlooked is quite small. In addition, the proportions of service members still on active duty on two specified dates were similar for deployed and nondeployed veterans. The data were most complete for the period immediately after the Gulf War, when any potentially teratogenic effects of service in the Gulf War might be expected to have been observed. Because measures of Gulf War service and birth outcomes were independent of one another, it is unlikely that there was any systematic bias due to overdiagnosing or underdiagnosing in either group.

Consideration must be given to the potential for bias due to underascertainment of births and birth defects. As indicated, the numbers on active duty on two specified dates one year apart were very similar for the Gulf War and the nondeployed veterans, both men and women. The slight differences in the number lost to follow-up were not likely to be major sources of bias. Similarly, failure to identify births because they took place in nonmilitary hospitals was not likely to be the source of important bias, since the proportion of such births among male Gulf War veterans was slightly lower than among male nondeployed veterans; among female service members, es-

TABLE 5. MOST COMMON (5 PERCENT OR MORE OF TOTAL) SEVERE CONGENITAL ANOMALIES AMONG CHILDREN OF MALE SERVICE MEMBERS.

DIAGNOSTIC GROUPING (ICD-9-CM CODES)	RANK	TOTAL NO.	% OF ALL SEVERE DEFECTS	CHILDREN OF GULF WAR VETERANS		CHILDREN OF NONDEPLOYED VETERANS		RELATIVE RISK (95% CI)*
				FREQUENCY	RISK (%)	FREQUENCY	RISK (%)	
Hypospadias and epispadias (752.6)	1	255	22.40	125	0.41	130	0.40	1.04 (0.81–1.33)
Selected congenital anomalies of the circulatory system (747.0, 747.10, 747.3)	2	210	18.47	106	0.35	104	0.32	1.10 (0.84–1.45)
Selected bulbus cordis and cardiac septal-closure anomalies (745.0, 745.10, 745.11, 745.12, 745.19, 745.2, 745.4, 745.5, 745.60, 745.61, 745.69)	3	204	18.00	78	0.26	126	0.39	0.67 (0.51–0.89)
Congenital hip dislocation (754.30, 754.31, 754.35)	4	137	12.05	75	0.25	62	0.19	1.31 (0.94–1.83)
Selected urinary anomalies (753.0, 753.2, 753.5, 753.6)	5	94	8.27	41	0.14	53	0.16	0.84 (0.56–1.26)
Selected chromosomal anomalies (758.0, 758.1, 758.2)	6	64	5.63	30	0.10	34	0.10	0.96 (0.58–1.56)

*CI denotes confidence interval.

TABLE 6. MOST COMMON (5 PERCENT OR MORE OF TOTAL) SEVERE CONGENITAL ANOMALIES AMONG CHILDREN OF FEMALE SERVICE MEMBERS.

DIAGNOSTIC GROUPING (ICD-9-CM CODES)	RANK	TOTAL NO.	% OF ALL SEVERE DEFECTS	CHILDREN OF GULF WAR VETERANS		CHILDREN OF NONDEPLOYED VETERANS		RELATIVE RISK (95% CI)*
				FREQUENCY	RISK (%)	FREQUENCY	RISK (%)	
Hypospadias and epispadias (752.6)	1	61	22.02	19	0.49	42	0.48	1.04 (0.60–1.78)
Selected congenital anomalies of the circulatory system (747.0, 747.10, 747.3)	2	57	21.51	16	0.42	41	0.46	0.90 (0.50–1.59)
Selected bulbus cordis and cardiac septal-closure anomalies (745.0, 745.10, 745.11, 745.12, 745.19, 745.2, 745.4, 745.5, 745.60, 745.61, 745.69)	3	43	16.23	7	0.18	36	0.41	0.45 (0.20–1.00)
Congenital hip dislocation (754.30, 754.31, 754.35)	4	32	12.08	12	0.31	20	0.23	1.38 (0.67–1.81)
Selected urinary anomalies (753.0, 753.2, 753.5, 753.6)	5	18	6.79	6	0.16	12	0.14	1.15 (0.43–3.05)
Selected neural-tube defects (740.0, 740.1, 741.0, 741.9, 742.0, 742.1, 742.3)	6	14	5.28	3	0.08	11	0.12	0.63 (0.17–2.24)
Selected chromosomal anomalies (758.0, 758.1, 758.2)	6	14	5.28	4	0.10	10	0.11	0.92 (0.29–2.92)

*CI denotes confidence interval.

sentially all the identified births occurred in military hospitals. We cannot address the potential for bias due to failure to count births among reserve-component soldiers, because we have no information on births to these service members.

We have no reason to suspect that there was a difference in failure to identify birth defects between the exposure groups, but a nondifferential misclassification would have resulted in a bias toward the null. Calle and Khoury[15] found that most minor and 28 percent of major defects were not noted in discharge records. Because they considered a defect "missed" if the diagnostic code on the discharge record did not match the medical record at the four-digit ICD-9-CM code level, we believe that our accounting is probably more accurate. Since our findings were similar for "any defect" as well as for "severe defects," even for diagnoses such as congenital hip dis-

location, which Calle and Khoury found were well-reported, we believe that failure to identify anomalies was not a substantial source of bias.

For several reasons, we recommend a conservative approach in interpreting these data. Although hospital birth records have been used for surveillance of birth defects[16] and are useful for rapid analysis of trends in large populations, such use has two major limitations. First, not all congenital defects are evident at birth; some are detected months or years later and thus cannot be included in a study limited to birth records. Second, some patterns of congenital malformations occurring as syndromes are not well defined by the ICD-9-CM system. We have relied on existing administrative data bases for this epidemiologic research.[17] The potential pitfalls presented by Kuller[17] include overinterpretation of the data and the identification of spurious associations; there can also be a tendency to generate hypotheses requiring further study, even if the initial observations are based on inadequate information or the associations are biologically implausible.

In conclusion, this report provides substantial evidence that the children of Gulf War veterans do not have an increased risk of birth defects.

The opinions expressed in this article are those of the authors and not necessarily those of the U.S. Army, U.S. Navy, or U.S. Department of Defense.

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