

Appendix

Presentation 1- Maria Araneta

**Birth Defects and Pregnancy Outcomes
Following Service in the Gulf War**

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October 27, 2003

Meeting of the Research Advisory Committee
on Gulf War Veterans' Illnesses

**Prevalence of Birth Defects Among
Infants of Gulf War Veterans in Arkansas,
Arizona, California, Georgia, Hawaii, and
Iowa, 1989-1993**

*Birth Defects Research (Part A): Clinical and
Molecular Teratology 2003: 67;246-260*

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Background

- U.S. General Accounting Office: 21 teratogens and reproductive toxicants present in the GW environment
- *Oil fires and soil:*
 - arsenic benzene benzopyrene
 - cadmium lead mercury
 - nickel toluene xylene
 - di-n-butyl phthalate hexachlorobenzene
 - hexachloroethane pentachlorophenol
 - hexachlorocyclopentadiene
- *Pesticides:*
 - carbaryl diazinon dichlorvos
 - ethanol lindane warfarin
- *Decontaminating agents:*
 - ethylene glycol monomethyl ether

Previous studies

- *Penman, 1996: 2 National Guard units, 5 case infants*
- *Cowan, 1997: military hospitals, newborn diagnoses only, ICD-9 codes*
- *Araneta, 1997: Goldenhar syndrome, military hospitals, rare condition*
- *Goss Gilroy, Inc. 1998: Canada, self-reported, ↑ birth defects among GWV infants*
- *Kang, 2001: self-reported, not validated against medical records, ↑ birth defects among GWV infants*

States with Active Surveillance for Birth Defects



Active Case Ascertainment for Birth Defects

1. Population-based
 - includes military and non-military hospitals
 - births to Reservists and National Guard members
 - births to former military personnel
2. Surveillance through infant's 1st birthday
 - Captures 95%-99% of birth defects

Active surveillance of Birth Defects

3. Data abstracted from multiple sources:
 - outpatient clinics* *hospitals*
 - cytogenetic laboratories* *genetic clinics*
 - cardiac catheterization logs* *surgical logs*
 - molecular biology laboratories*
4. Birth defects recorded by CDC's 6-digit code for Reportable Congenital Anomalies
5. Provides more complete case ascertainment and morphologic classification of birth defects

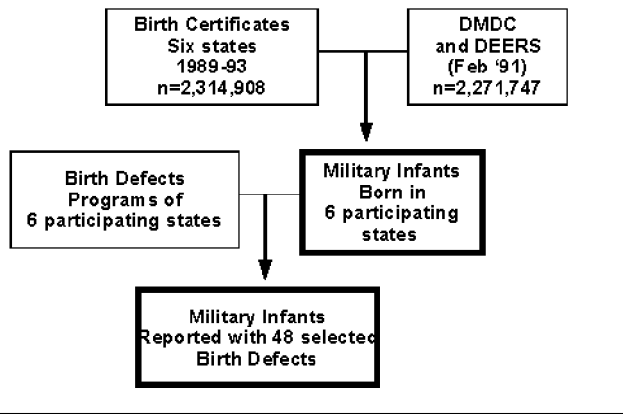
Objectives

- Identify infants born to military personnel between 1989-93 in states with active surveillance of birth defects
- Measure the prevalence of selected birth defects
 - a) GWV and NDV infants
 - prewar conceptions
 - postwar conceptions
 - b) GWV infants
 - prewar vs. postwar conceptions

Methods - Data Sources

- Military:
- Defense Manpower Data Center (DMDC) - *military sponsor data*
 - Defense Eligibility Enrollment Reporting System (DEERS) – *spouse, children*
- Arkansas, Arizona, California, Georgia, Hawaii, Iowa:
- Vital records - *birth certificates*
 - Birth Defects Programs - *birth defects data*

Military Infants in the participating states Birth Defects Registries



48 Selected Birth Defects

- | | |
|-----------------------------|---------------------|
| Anencephalus | Spina Bifida |
| Hydrocephalus | Encephalocele |
| Microcephalus | |
| Aniridia | Congenital cataract |
| Anophthalmia/microphthalmia | |
| Anotia/microtia | |
| Cleft palate | Cleft lip |

48 Selected Birth Defects (continued)

Common truncus	Tetralogy of Fallot
Ventricular septal defect	Ebstein's anomaly
Aortic valve stenosis	Coarctation of aorta
Pulmonary valve atresia/stenosis	
Pulmonary valve insufficiency	
Endocardial cushion defect	
Pulmonary artery anomalies	
Transposition of great arteries	
Tricuspid atresia/stenosis	
Tricuspid valve insufficiency	
Hypoplastic left heart syndrome	

48 Selected Birth Defects (continued)

Lung agenesis/hypoplasia	Choanal atresia
Pyloric stenosis	Hirschsprung disease
Biliary atresia	Gastroschisis
Diaphragmatic hernia	Omphalocele
Hypospadias/epispadias	Bladder exstrophy
Renal agenesis/hypoplasia	
Obstructive genitourinary defect	
Esophageal atresia/tracheoesophageal fistula	
Rectal/large intestinal atresia/stenosis	

48 Selected Birth Defects (continued)

Reduction deformity - upper limbs, lower limbs
Trisomy 13 (Patau syndrome)
Trisomy 18 (Edward syndrome)
Trisomy 21 (Down syndrome)

Fetal alcohol syndrome	Amniotic bands
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Dextrocardia *Chromosomal anomalies*
Goldenhar syndrome (oculoauriculovertebral complex)

Estimates of Prewar and Postwar Conceptions

Prewar conceptions:

GWV: Infant's DOB \leq Mother's deployment date

Infant's DOB - gest. age \leq Father's deploy date

NDV: Conceived \leq December 31, 1990

Postwar conceptions:

GWV: Infant's DOB $>$ Mother's deployment date

Infant's DOB - gest. age \geq Father's return date

NDV: Conceived \geq January 1, 1991

Table 1. Demographic Characteristics of Infants Born to Women Military Personnel, 1989-93

	<u>GWV</u> <u>(n=450)</u>	<u>NDV</u> <u>(n=3,966)</u>
Male	48%	50%
Birthweight (gms)	3,351	3,341
Preterm birth (<37 wks)	9%	9%
Maternal age (yrs)	25.3	25.9 [*]
Paternal age (yrs)	27.2	27.5
White	51%	60% [*]
≤ High school	55%	53%
Unmarried	28%	23% [*]

^{*}p-value<0.05 (statistically significant)

Demographic Characteristics of Infants Born to Women Military Personnel, 1989-93

	<u>GWV</u> <u>(n=450)</u>	<u>NDV</u> <u>(n=3,966)</u>
Smoking	7%	9%
Alcohol	1%	1%
Prenatal visits	11.2	11.7 [*]
Army	64%	35% [*]
Marine Corps	11%	5% [*]
Reservist/Natl Guard	24%	12% [*]
Military Officers	8%	11% [*]

^{*}p-value<0.05

Table 2. Demographic Characteristics of Infants Born to Male Military Personnel, 1989-93

	<u>GWV</u> <u>(n=11,511)</u>	<u>NDV</u> <u>(n=29,086)</u>
Birthweight (gms)	3,367	3,389 [*]
Maternal age (yrs)	25.3	26.0 [*]
Paternal age (yrs)	26.6	27.5 [*]
White (mother)	59%	63% [*]
≤ High school (mother)	56%	51% [*]
Unmarried	10%	7% [*]
Prior live births	0.8	0.9 [*]
Multiple births	1.8	2.4 [*]

^{*}p-value<0.05

Demographic Characteristics of Infants Born to Male Military Personnel, 1989-93

	<u>GWV</u> <u>(n=450)</u>	<u>NDV</u> <u>(n=3,966)</u>
Marine Corps	28%	11% [*]
Enlisted personnel	83%	78% [*]

^{*}p-value<0.05

Table 3. Selected Birth Defects Prevalence* among Prewar conceptions to Women GWVs and NDVs, 1989-91

	GWV (n=142)	NDV (n=2,007)	RR (95% CI)
Hydrocephalus	1 (70)	2 (10)	7.1 (0.6-79)
VSD	0	11 (55)	
Obstructive genitourinary defect	0	6 (30)	
Pyloric stenosis	0	5 (30)	
Hypospadias	0	5 (30)	
Tetralogy of Fallot	0	4 (20)	
Cleft lip w/o c.palate	0	3 (15)	

*per 10,000 live births

Table 4. Selected Birth Defects Prevalence* among Prewar conceptions to Male GWVs and NDVs, 1989-91

	GWV (n=6,863)	NDV (n=17,922)	RR (95% CI)
Hypospadias	22 (32)	51 (29)	1.1 (0.7 - 1.9)
Pyloric stenosis	14 (20)	25 (14)	1.5 (0.8 - 2.8)
VSD	13 (19)	45 (25)	0.8 (0.4 - 1.4)
Obstructive genitourinary defects	9 (13)	29 (16)	0.8 (0.4 - 1.7)
Down syndrome	9 (13)	21 (12)	1.1 (0.5 - 2.5)
Tricuspid valve insufficiency	8 (18)	24 (20)	0.9 (0.4 - 2.0)
Aortic valve stenosis	0	4 (2)	

*per 10,000 live births

Table 5. Selected Birth Defects Prevalence* Among Postwar Conceptions to Women GWVs and NDVs, 1991-93

	GWV (n=308)	NDV (n=1,959)	RR (95% CI)
Hydrocephalus	1 (32)	1 (5)	6.4 (0.2 - 189)
VSD	1 (32)	7 (36)	0.9 (0.05 - 5.5)
Pulm valve atresia	1 (32)	1 (5)	6.4 (0.2 - 189)
Cleft lip	1 (32)	1 (5)	6.4 (0.2 - 189)
Hypospadias	4 (130)	4 (20)	6.4 (1.5 - 27) [†]
Renal agenesis	1 (32)	3 (15)	2.1 (0.1 - 18)
Obst genitourinary	1 (32)	8 (41)	0.8 (0.04 - 4.7)
Down syndrome	1 (32)	0	

*per 10,000 live births; [†]p = 0.015

Table 6. Selected Birth Defects Prevalence* Among Postwar Conceptions to Male GWVs and NDVs, 1991-93

	GWV (n=4,648)	NDV (n=11,164)	RR (95% CI)
Hypospadias	15 (32)	35 (31)	1.0 (0.6 - 2)
VSD	10 (21)	36 (32)	0.7 (0.3 - 1)
Tricuspid valve insufficiency**	10 (29)	9 (11)	2.7 (1.1 - 7) [†]
Obst genitourinary	9 (19)	21 (19)	1.0 (0.5 - 2)
Pyloric stenosis	7 (15)	18 (16)	0.9 (0.4 - 2)
Aortic valve stenosis	5 (11)	2 (2)	6.0 (1.2 - 31) [‡]
Coarctation of aorta	5 (11)	3 (3)	4.0 (0.96-17)
Renal agenesis	5 (11)	5 (4)	2.4 (0.7 - 8)

*per 10,000 live births, ** California births excluded,
[†]p=0.039, [‡]p=0.026

Table 7. Selected Birth Defects Prevalence* Among Prewar vs. Postwar conceptions to Women GWVs, 1989-93

	Postwar (n=308)	Prewar (n=142)	RR (95%CI)
Hydrocephalus	1 (32)	1 (70)	0.5 (0.03 - 7)
VSD	1 (32)	0	
Pulm valve atresia	1 (32)	0	
Cleft lip	1 (32)	0	
Hypospadias	4 (130)	0	
Renal agenesis	1 (32)	0	
Obst genitourinary	1 (32)	0	
Down syndrome	1 (32)	0	

*per 10,000 live births

Table 8. Selected Birth Defects Prevalence* Among Prewar vs. Postwar conceptions to Male GWVs, 1989-93

	Postwar (n=4,648)	Prewar (n=6,863)	RR (95%CI)
Hypospadias	15 (32)	22 (32)	1.0 (0.5 - 2)
VSD	10 (21)	13 (19)	1.1 (0.5 - 3)
Tricuspid valve insufficiency**	10 (29)	8 (18)	1.6 (0.6 - 4)
Obst genitourinary	9 (19)	9 (13)	1.5 (0.6 - 4)
Pyloric stenosis	7 (15)	14 (20)	0.7 (0.2 - 2)
Aortic valve stenosis	5 (11)	0	16 (0.9 - 294)†
Coarctation of aorta	5 (11)	1 (2)	7.4 (0.9 - 63)
Renal agenesis	5 (11)	0	16 (0.9 - 294)†

*per 10,000 live births; †p<0.011 logit estimator

Adjusted Prevalence – cardiovascular defects

↑ tricuspid valve insufficiency and aortic valve stenosis did not differ when adjusted by:

- State
- Maternal and paternal age
- Ethnicity
- Marital Status
- Education
- Parity, multiple births
- Prenatal visits
- Military branch, rank

Adjusted Prevalence – hypospadias

↑ Prevalence of hypospadias persisted after adjustment for:

- Paternal age
- Small for gestational age
- Low birth weight
- Preeclampsia
- Low parity

Adjusted Prevalence – renal agenesis or hypoplasia

- ↑ Prevalence of renal agenesis/hypoplasia persisted after adjustment for:
- Prenatal alcohol
 - Intrauterine growth retardation

Conclusions

- Linkage of military and state health department records enables measurement of the prevalence of birth defects among infants:
 - Through infant's 1st year of life
 - in military and civilian hospitals
 - Reservists and National Guard members
 - former and current military personnel
- Higher prevalence of tricuspid valve insufficiency, aortic valve stenosis, and renal agenesis/hypoplasia in postwar infants of GWV men.

Conclusions

- Higher prevalence of hypospadias among postwar infants of GWV women.
- The etiology of birth defects is unknown for 70% of all birth defects
- We did not have the ability to determine if the excess risk of birth defects was caused by inherited, environmental, or synergistic factors, or was due to chance.

Limitations

- California: no access to military hospitals
- Limited to live births
- Birth defects diagnosed after first birthday not included (1% - 5%)
- Statistical power
- Multiple comparisons

Statistical Power

<u>Condition</u>	<u>Optimum sample size</u>	<u>Available</u>
Hypospadias	257	154
Statistical power	80%	67%
Tricuspid valve insuff.	6373	4648

Multiple Comparisons

<u>Comparisons</u>	<u>Expected</u>	<u>Observed</u>
Postwar GWV vs NDV women		
7 birth defects	0.35	1
Postwar GWV vs NDV men		
26 birth defects	1.3	2
Postwar GWV vs prewar GWV men		
24 birth defects	1.2	2

Conception and Pregnancy during the Persian Gulf War: The Risk to Women Veterans

Annals of Epidemiology, November 2003

Araneta MRG, Kamens DR, Zau AC, Gastanaga VM, Schlangen KM, Hiliopoulos KM, Gray GC.

Purpose

To characterize reproductive outcomes:

- Live births
 - Stillbirths
 - Spontaneous abortions
 - Ectopic pregnancies
 - Induced abortions
- among women who were pregnant while deployed to the Gulf War

Methods

- Deployment data + inpatient records (153 military hospitals) were used to identify servicewomen who were:
 - pregnant between August 1990 and May 1992
 - belonged to UIC deployed to the Gulf War
- Postal surveys in 1997-98 to elicit reproductive history + individual deployment dates
- Validated self-reported outcomes against military hospitalization records

Results

- 3285 women had a pregnancy-related admission in a military hospital
- 1558 completed the questionnaire

Dates of delivery (or fetal loss), weeks of gestation, and individual deployment dates identified:

415 Gulf-war exposed pregnancies
298 GWV postwar conceptions
427 NDV conceptions

Results

- The prevalence of stillbirths, spontaneous abortions, ectopic pregnancies, and induced abortions were similar among GWV-exposed pregnancies and NDV conceptions.
- Spontaneous abortions were significantly higher among postwar GWV conceptions (22.8%) compared to NDV conceptions (9.1%, adjusted OR: 2.92, 95% CI: 1.9 – 4.6)
- Ectopic pregnancies were significantly higher among postwar GWV conceptions (10.7%) compared to NDV conceptions (1.4%, adjusted OR: 7.7, 95% CI: 3.0 - 20)

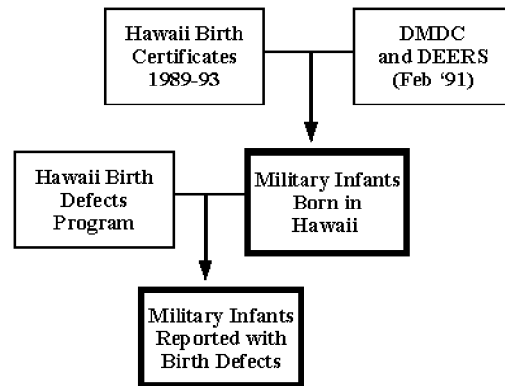
Conclusions

- Among women veterans who belonged to units that were deployed to the Gulf War:
- GWV-exposed conceptions and nondeployed conceptions had similar reproductive outcomes.
- However, GWV postwar conceptions were at increased risk for ectopic pregnancies and spontaneous abortions

Selection of Hawaii for Pilot Site

- Large military population
 - 20% of births have a military parent
- Same genetic referral site for military and civilian hospitals
- Parental SSN on birth certificate
- Military employment on birth certificate

Military Infants Reported to the Hawaii Birth Defects Program



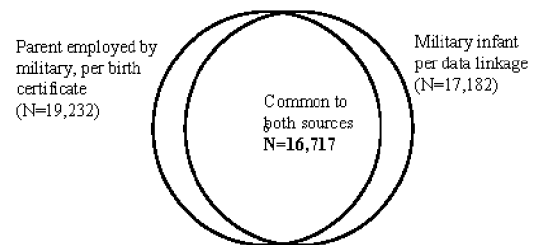
How to improve statistical power? How to reduce multiple comparisons?

	GWV (n=4,956)	NDV (n=13,123)	RR (95%CI)
Tricuspid valve insufficiency**	10 (27)	10 (10)	2.6 (1.1 – 6.4) [†]
Aortic valve stenosis	5 (10)	2 (1.5)	6.6 (1.4 - 45) [‡]
Coarctation of aorta	5 (10)	3 (2)	4.4 (1.1 - 21) [§]

*per 10,000 live births, ** California births excluded,
[†]p=0.023, [‡]p=0.019, [§]p=0.04

27 comparisons, expect 5% (1.4) to differ due to chance, observe differences in 3

Enumeration of Military Infants: Military Employment on Birth Certificate vs. Linkage Method, Live Births, Hawaii, 1989-93



Sensitivity = 87% Specificity = 99% Positive Predictive Value = 97%